JC17 Rec'd PCT/PTO 13 APR 2001

FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
VOSS1160

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
09/807499

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/07604	**October 11, 1999**	**October 13, 1998**

TITLE OF INVENTION
NON-DESENSITIZING AMPA-RECEPTORS

APPLICANT(S) FOR DO/EO/US
Christian Rosenmund, Sebastian Russo, Manahem Neuman, Yael Stern-Bach

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☒ has been transmitted by the International Bureau.
   - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☐ have been transmitted by the International Bureau.
   - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Sequence Statement
Sequence Listing in Computer Readable Format
Sequence Listing in written form
Postcard
Express Mail Label No.: EL617037862US

JC02 Rec'd PCT/PTO 13 APR 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/807499	PCT/EP99/07604	VOSS1160

21. The following fees are submitted:.

	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO **$840.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$690.00**		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**		
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$840.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	69 - 20 =	49	x $18.00	**$882.00**	
Independent claims	2 - 3 =	0	x $78.00	**$0.00**	
Multiple Dependent Claims **(check if applicable).**			☒	**$260.00**	
TOTAL OF ABOVE CALCULATIONS =				**$1,982.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).**			☒	**$991.00**	
SUBTOTAL =				**$991.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
TOTAL NATIONAL FEE =				**$991.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	**$0.00**	
TOTAL FEES ENCLOSED =				**$991.00**	
				Amount to be: refunded	$
				charged	$

☒ A check in the amount of **$991.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees. A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Lisa A. Haile, Ph.D.
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1600
San Diego, CA 92121-2189

Lisa A. Haile

SIGNATURE

Lisa A. Haile, Ph.D.

NAME

38,347

REGISTRATION NUMBER

13 April 2001

DATE

09/807499

JC02 Rec'd PCT/PTO 13 APR 2001

PATENT
Attorney Docket No.: VOSS1160

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Rosenmund et al.	Art Unit:	Unassigned
Application No.:		Examiner	Unassigned
Filed:	13 April 2001		
Title:	NON-DESENSITIZING AMPA-RECEPTOR		

Commissioner for Patents
Washington, D.C. 20231
BOX PCT

STATEMENT UNDER 37 C.F.R. §§ 1.821(f) and (g)

Sir:

I hereby state, as required by 37 C.F.R. § 1.821(f), that the information recorded in computer readable form is identical to the written sequence listing.

I hereby state that the submission, filed in accordance with 37 C.F.R. § 1.821 (g), herein does not include new matter.

Respectfully submitted,

Date: 4/13/01

Lisa A. Haile

Lisa A. Haile, Ph.D.
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I hereby certify that this paper is being deposited with the United States Postal Service "EXPRESS MAIL Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to BOX PATENT APPLICATION, Commissioner of Patents and Trademarks; Washington, DC 20231.

Mikhail Bayley

Mikhail Bayley

Gray Cary\GT\6233367.1
105032-990000

09/807499
JC02 Rec'd PCT/PTO 1 3 APR 2001

PATENT
ATTY. DOCKET NO. VOSS1160

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Christian Rosenmund et al.	Art Unit:	Unassigned
Serial No.:	Unassigned	Examiner	Unassigned
Filed:	Herewith based on PCT/EP99/07604		
Title:	NON-DESENSITIZING AMPA-RECEPTORS		

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to examination of the above-identified patent application, entry of the amendments and consideration of the following remarks are respectfully requested.

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

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DATE OF DEPOSIT April 13, 2001 I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 C F R 1 10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D C 20231

Mikhail Bayley
(TYPED OR PRINTED NAME OF PERSON MAILING PAPER OR FEE)

Mikhail Bayley

SIGNATURE OF PERSON MAILING PAPER OR FEE)

Gray Cary\GT\6233378.1
105032-990000

I. AMENDMENTS

Claims 3-8, 10, 17-18, 21, 25-34 and 37 have been amended.

Please cancel claim 36 without prejudice.

Please amend the claims as follows:

3. (Amended) The nucleic acid molecule of claim 1 [or 2] wherein the (poly)peptide comprises an aromatic amino acid at position 497 of SEQ ID NO:1 , 5 or 9, at position 504 of SEQ ID NO: 2, 6, or 10, at position 507 of SEQ ID NO: 3, at position 505 of SEQ ID NO: 4 or 8 or at position 513 of SEQ ID NO: 7, but differs therefrom by at least one mutation selected from the group consisting of amino acid substitutions, addition(s) insertions, deletions, inversions and/or duplications.

4. (Amended) The nucleic acid molecule of [any one of] claim[s] 1 [to 3] derived from a rat, a mouse or a human.

5. (Amended) The nucleic acid molecule of [any one of] claim[s] 1 [to 4], wherein said aromatic amino acid residue is tyrosine, phenylalanine, tryptophan or histidine.

6. (Amended) The nucleic acid molecule of [any one of] claim[s] 1 [to 5] which is DNA, RNA or PNA.

7. (Amended) The nucleic acid molecule of [any one of] claim[s] 1 [to 6] encoding a fusion protein.

8. (Amended) A vector comprising the nucleic acid molecule of [any one of] claim[s] 1 [to 7].

10. (Amended) A host transformed with a vector of claim 8 [or 9] or comprising the nucleic acid of claim 1 [to 7].

17. (Amended) A method for producing [the] a (poly)peptide encoded by a nucleic acid molecule of [any one of] claim[s] 1 [to 7] comprising culturing [raising the] a host [of any one of claims 10 to 16] transformed with a vector containing a nucleic acid molecule of claim 1 and isolating the produced (poly)peptide.

18. (Amended) A (poly)peptide encoded by the nucleic acid molecule of [any one of] claim[s] 1 [to 7 or produced by the method of claim 17].

21. (Amended) A composition comprising [the] a nucleic acid molecule of [any one of] claim[s] 1 [to 7], [the] a vector of claim 8 [or 9], [the] a (poly)peptide of claim 18 and/or [the] an antibody of claim 19 [or 20].

25. (Amended) A method of identifying molecules which are capable of interacting with glutamate receptors of the AMPA-type, comprising the steps of

(a) contacting a non-desensitizing AMPA-receptor as encoded by a nucleic acid molecule of [any one of] claim[s] 1 [to 7], a vector of claim[s] 8 [or 9], a host of [any one of] claim[s] 10 [to 16], or an antibody of claim 19 [or 20] with said molecule; and
(b) identifying among these molecules the molecules which are capable of interacting with said glutamate receptors of the AMPA-type.

26. (Amended) A method for the characterization of molecules which are capable of interaction with glutamate receptors of the AMPA-type, comprising the steps of

(a) contacting a non-desensitizing AMPA-receptor as defined in [any one of] claim[s] 1 [to 7], a vector of claim[s] 8 [or 9], a host of [any one of] claim[s] 10 [to 16], or an antibody of claim 19 [or 20] with said molecules; and

(b) measuring and/or detecting the characteristic effect said molecules evoke.

27. (Amended) A method of screening for molecules which are capable of interacting with glutamate receptors of the AMPA-type, comprising the steps of

(a) contacting a non-desensitizing AMPA-receptor as encoded by a nucleic acid molecule of [any one of] claim[s] 1 [to 7], a vector of claim 8 [or 9] or a host of [any one of] claim[s] 10 [to 16] with a candidate molecule; and

(b) measuring and/or detecting a response; and

(c) comparing said response to a standard response as measured in the absence of said candidate molecule.

28. (Amended) A method for the production of a pharmaceutical composition comprising the steps of the method of [any one of] claim[s] 25 [to 27] and comprising a further step, wherein a derivative of said identified, characterized and/or screened molecule is generated.

29. (Amended) A method for the production of a pharmaceutical composition comprising the steps of the method of [any one of] claim[s] 25 [to 28] and formulating the molecules identified, characterized, screened and/or derivatized in pharmaceutically acceptable form.

30. (Amended) The method of [any one of] claim[s] 25 [to 29], wherein said molecule(s) comprise(s) (a) neuroprotective and/or (a) nootropic molecule(s).

31. (Amended) The method of [any one of] claim[s] 25 [to 30], wherein said molecule(s) comprise(s) antagonist(s), partial antagonist(s), partial agonist(s) and/or agonist(s) for glutamate receptors.

32. (Amended) Use of a non-desensitizing AMPA-receptor as encoded by the nucleic acid molecule of [any one of] claim[s] 1 [to 7] or use of a host as defined in [any one of] claim[s] 10 [to 16] as a biosensor for glutamate concentrations.

33. (Amended) Use of a non-desensitizing AMPA-receptor as encoded by the nucleic acid molecule of [any one of] claim[s] 1 [to 7] or use of a host as defined in [any one of] claim[s] 10 [to 16] for the characterization of glutamate receptor channel properties.

34. (Amended) Use of a nucleic acid molecule of [any one of] claim[s] 1 [to 7], of a vector of claim[s] 8 [or 9], of a host of claim[s] 10 [or 11], of a (poly)peptide of claim 18 and/or of the antibody of claim 19 [or 20] for the preparation of a pharmaceutical composition for preventing and/or treating neurological and/or neurodegenerative disorders.

36. (Canceled)

37. (Amended) A kit comprising the nucleic acid molecule of [any one of] claim[s] 1 [to 7], the vector of claim 8 [or 9], the host of [any one of] claim[s] 11 [to 16], the (poly)peptide of claim 18, the antibody of claim 19 [or 20] or the molecule as identified, characterized or screened in [any one of] claim[s] 25 [to 31].

II. REMARKS

Claims 1-35 and 37 are pending. For the Examiner's convenience, a copy of the claims as they will stand upon entry of the present amendment is attached hereto as Exhibit A.

Claims 3-8, 10. 17-18, 21, 25-34 and 37 were amended, which previously were multiple dependent claims, have been amended to single dependency. The amendments merely address a formality and do not add new matter.

Applicants submit that the amended claims are in condition for allowance and respectfully request that the Examiner issue a notice to that effect. The Examiner is invited to contact Applicants' undersigned attorney if there are any questions relating to the subject application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Lisa A. Haile

Date: 4/13/01

Lisa A. Haile, Ph.D.
Reg. No. 38,347
Attorney for Applicant
Telephone No.: (858) 677-1456
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San Diego, California 92121-2189

Enclosure: Exhibit A

EXHIBIT A

CLAIMS UPON ENTRY OF THE AMENDMENT

1. A nucleic acid molecule encoding a (poly)peptide which has an amino acid sequence of a glutamate receptor of the AMPA-type and/or of a subunit of said receptor and functions as a non-desensitizing AMPA-receptor or as a non-desensitizing subunit thereof, wherein the leucine corresponding to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ is replaced by an aromatic amino acid.

2. The nucleic acid molecule of claim 1 which is

   (a) a nucleic acid molecule comprising a nucleic acid molecule encoding the (poly)peptide having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10, wherein the leucine residue corresponding to position 497 of SEQ ID NO: 1, 5 or 9, corresponding to position 504 of SEQ ID NO: 2, 6 or 10, corresponding to position 507 of SEQ ID NO: 3, to position 505 of SEQ ID NO: 4 or 8, or corresponding to position 513 of SEQ ID NO: 7 is replaced by an aromatic amino acid;

   (b) a nucleic acid molecule comprising a nucleic acid molecule having the DNA sequence of SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 or SEQ ID NO: 20, wherein the codon represented by nnn corresponds to a codon coding for an aromatic amino acid;

(c) a nucleic acid molecule hybridizing to the complementary strand of a nucleic acid molecule of (a) or (b);

(d) a nucleic acid molecule being degenerate as a result of the genetic code to the nucleotide sequence of a nucleic acid molecule as defined in (c).

3. (Amended) The nucleic acid molecule of claim 1 wherein the (poly)peptide comprises an aromatic amino acid at position 497 of SEQ ID NO:1 , 5 or 9, at position 504 of SEQ ID NO: 2, 6, or 10, at position 507 of SEQ ID NO: 3, at position 505 of SEQ ID NO: 4 or 8 or at position 513 of SEQ ID NO: 7, but differs therefrom by at least one mutation selected from the group consisting of amino acid substitutions, addition(s) insertions, deletions, inversions and/or duplications.

4. (Amended) The nucleic acid molecule of claim 1 derived from a rat, a mouse or a human.

5. (Amended) The nucleic acid molecule of claim 1, wherein said aromatic amino acid residue is tyrosine, phenylalanine, tryptophan or histidine.

6. (Amended) The nucleic acid molecule of claim 1 which is DNA, RNA or PNA.

7. (Amended) The nucleic acid molecule of claim 1 encoding a fusion protein.

8. (Amended) A vector comprising the nucleic acid molecule of claim 1.

9. A vector of claim 8 which is an expression vector, a gene targeting vector and/or a gene transfer vector.

10. (Amended) A host transformed with a vector of claim 8 or comprising the nucleic acid of claim 1.

11. The host of claim 10 which is a mammalian cell, an amphibian cell, an insect cell, a fungal cell, a plant cell or a bacterial cell.

12. The host of claim 11, wherein said mammalian cell is a HEK cell.

13. The host of claim 11, wherein said amphibian cell is an oocyte.

14. The host of claim 13, wherein said oocyte is a frog oocyte.

15. The host of claim 10 which is a non-human transgenic organism.

16. The host of claim 15, wherein said non-human organism is a mammal, amphibian, an insect, a fungus or a plant.

17. (Amended) A method for producing a (poly)peptide encoded by a nucleic acid molecule of claim 1 comprising culturing a host transformed with a vector containing a nucleic acid molecule of claim 1 and isolating the produced (poly)peptide.

18. (Amended) A (poly)peptide encoded by the nucleic acid molecule of claim 1.

19. An antibody specifically directed to the (poly)peptide of claim 18, wherein said antibody specifically reacts with an epitope comprising the aromatic amino acid which replaces the leucine at position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of said wildtype rat AMPA receptor $GluR1_{flip}$.

20. The antibody of claim 19 which is a monoclonal antibody.

21. (Amended) A composition comprising a nucleic acid molecule of claim 1, a vector of claim 8, a (poly)peptide of claim 18 and/or an antibody of claim 19.

22. The composition of claim 21 which is a pharmaceutical composition, optionally further comprising a pharmaceutically acceptable carrier and/or diluent and/or excipient.

23. The composition of claim 21 which is a diagnostic composition, optionally further comprising suitable means for detection.

24. A method for the blocking of desensitation of glutamate receptor of the AMPA-type, comprising the step of replacing a leucine corresponding to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ by an aromatic amino acid.

25. (Amended) A method of identifying molecules which are capable of interacting with glutamate receptors of the AMPA-type, comprising the steps of
   (a) contacting a non-desensitizing AMPA-receptor as encoded by a nucleic acid molecule of claim 1, a vector of claim 8, a host of claim 10, or an antibody of claim 19 with said molecule; and
   (b) identifying among these molecules the molecules which are capable of interacting with said glutamate receptors of the AMPA-type.

26. (Amended) A method for the characterization of molecules which are capable of interaction with glutamate receptors of the AMPA-type, comprising the steps of
   (a) contacting a non-desensitizing AMPA-receptor as defined in claim 1, a vector of claim 8, a host of claim 10, or an antibody of claim 19 with said molecules; and
   (b) measuring and/or detecting the characteristic effect said molecules evoke.

27. (Amended) A method of screening for molecules which are capable of interacting with glutamate receptors of the AMPA-type, comprising the steps of
   (a) contacting a non-desensitizing AMPA-receptor as encoded by a nucleic acid molecule of claim 1, a vector of claim 8 or a host of claim 10 with a candidate molecule; and
   (b) measuring and/or detecting a response; and
   (c) comparing said response to a standard response as measured in the absence of said candidate molecule.

28. (Amended) A method for the production of a pharmaceutical composition comprising the steps of the method of claim 25 and comprising a further step, wherein a derivative of said identified, characterized and/or screened molecule is generated.

29. (Amended) A method for the production of a pharmaceutical composition comprising the steps of the method of claim 25 and formulating the molecules identified, characterized, screened and/or derivatized in pharmaceutically acceptable form.

30. (Amended) The method of claim 25, wherein said molecule(s) comprise(s) (a) neuroprotective and/or (a) nootropic molecule(s).

31. (Amended) The method of claim 25, wherein said molecule(s) comprise(s) antagonist(s), partial antagonist(s), partial agonist(s) and/or agonist(s) for glutamate receptors.

32. (Amended) Use of a non-desensitizing AMPA-receptor as encoded by the nucleic acid molecule of claim 1 or use of a host as defined in claim 10 as a biosensor for glutamate concentrations.

33. (Amended) Use of a non-desensitizing AMPA-receptor as encoded by the nucleic acid molecule of claim 1 or use of a host as defined in claim 10 for the characterization of glutamate receptor channel properties.

34. (Amended) Use of a nucleic acid molecule of claim 1, of a vector of claim 8, of a host of claim 10, of a (poly)peptide of claim 18 and/or of the antibody of claim 19 for the preparation of a pharmaceutical composition for preventing and/or treating neurological and/or neurodegenerative disorders.

35. The use of claim 33, wherein said neurological and/or neurodegenerative disorders are selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (FALS/SALS), ischemia, stroke, epilepsy, AIDS dementia and learning disorders.

37. (Amended) A kit comprising the nucleic acid molecule of claim 1, the vector of claim 8, the host of claim 11, the (poly)peptide of claim 18, the antibody of claim 19 or the molecule as identified, characterized or screened in claim 25.

Non-desensitizing AMPA-Receptors

The present invention relates to a nucleic acid molecule encoding a (poly)peptide which has an amino acid sequence of a glutamate receptor of the AMPA-type and functions as a non-desensitizing AMPA-receptor or as a non-desensitizing subunit thereof, wherein the leucine corresponding to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ is replaced by an aromatic amino acid. The invention further relates to (poly)peptides encoded by said nucleic acid molecules, vectors and hosts comprising said nucleic acid molecules, as well as to methods for producing (poly)peptides encoded by said nucleic acid molecules. The present invention also provides for antibodies specifically directed to (poly)peptides encoded by said nucleic acid molecules. Additionally, the invention relates to a method for the blocking of desensitization of a glutamate receptor of the AMPA-type, comprising the step of replacing a leucine which corresponds by comparison of homology to position 497 of the rat AMPA-receptor GluR1 by an aromatic amino acid and methods for identifying and/or characterizing molecules which are capable of interaction with glutamate receptors of the AMPA type. The invention also relates to the one of the aforementioned nucleic acid molecules, (poly)peptides, hosts, vectors and/or antibodies as biosensors, for the characterization of glutamate receptor channel properties and/or for the preparation of pharmaceutical compositions. Furthermore, the invention provides for pharmaceutical compositions, diagnostics and kits comprising and/or employing the compounds of the invention.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including any manufacturer's specifications, instructions,

etc.) are hereby incorporated by reference; however, there is no admission that any document cited is indeed prior art for patentability of the present invention.

Fast glutamatergic neurotransmission is a major contributor to cell-to-cell communication in the central nervous system. Approximately 90% of all synapses in the brain are glutamatergic.

Glutamate receptors are found throughout the mammalian brain, where they constitute the major excitatory transmitter system. The longest-known and best-studied glutamate receptors are ligand-gated ion channels, also called ionotropic glutamate receptors, which are permeable to cations. They have traditionally been classified into three broad subtypes based upon pharmacological and electrophysiological data: α-amino-3-hydroxy-5-methyl-4-isoaxole propionate (AMPA) receptors, kainate (KA) receptors, and N-methyl-D-aspartate (NMDA) receptors. Furthermore, a family of G protein-coupled glutamate receptors, which are also called metabotropic glutamate *trans*-1-aminiocyclopentane-1,3-dicarboxylate (tACPD) receptors, was identified (Sugiyama, Nature 325 (1987), 531-533).

At excitatory synapses, presynaptically released glutamate diffuses across the synaptic cleft, and binds to postsynaptically localized ionotropic glutamate receptors from the α-amino-3-hydroxy-5-methyl-4-isoazole propionate (AMPA), NMDA, and kainate receptor subtypes. The binding of glutamate somehow leads to a conformational change in the channel, thereby opening the pore and allowing the influx of cations into the postsynaptic cell. Longer exposures to glutamate result in desensitization of the channel, i.e. it resides in a long-lasting ligand-bound, yet shut state. Desensitization of AMPA and kainate receptors occurs within a few milliseconds, a value found to be on the time scale of the postsynaptic response. This remarkable fast rate, together with a slow recovery from desensitization, is thought to be one of the mechanisms modifying the processing of synaptic information (especially at synapses with multiple release zones), and

may serve as a negative feedback mechanism to prevent excitotoxic processes caused by excessive activation or brain damage that leads to prolonged glutamate exposure at the synaptic cleft. Recent molecular studies have provided increasing detailed models of the agonist binding site and of the channel pore (Reviewed by Green, Neuron 20 (1998), 427-444 and Pass, Trends Neurosci. 21 (1998), 117-125), however, little is known about structures underlying gating and desensitization.

There are four AMPA-selective subunits, GluR1-4 (or GluRA-RD), that can form functional distinct channels in homo- or hetero-oligomeric assemblies. The kainate receptors assemble from two pools: GluR5-7 and KA1-2 (reviewed by Seeburg, Trends Neurosci. 16 (1993), 359-365; Hollmann and Heinemann, Annu. Rev. Neurosci. 17 (1994), 31-108; Nakanishi and Masu, Annu. Rev. Biophys. Biomol. Struct. 23 (1994), 319-348). Recent topological studies divide the single subunit protein into several domains: (i) four hydrophobic domains, M1-M4, of which M1, M3 and M4 are thought to form transmembrane domains, while M2 forms a reentrant loop that lines the channel pore; (ii) a short cytoplasmic C-terminal domain, and (iii) two extracellular domains, composed of the N-terminus and the segment between M3-M4. Using a set of functional chimeric proteins made from the AMPA receptor GluR3 and the kainate receptor GluR6, it has been demonstrated that agonist binding specificity of these receptors is determined by two discontinuous segments, which were termed S1 and S2, respectively. S1 corresponds to a segment of ~150-amino acids preceding M1, and S2 to the segment between M3-M4 (Stern-Bach, Neuron 13 (1994), 1345-1357). Stimulated by the homology of S1-S2 to a set of bacterial periplasmic amino acid-binding proteins (PBPs), further specific residues within these segments, that bind agonists, and several structural models for the glutamate binding site have been constructed. According to these models, S1 and S2 form a bilobated structure that binds the agonist molecule in-between. S1 and the C-terminal half of S2 form the larger lobe 1, and the N-terminal half of S2 forms the smaller lobe 2. Recent crystallization of a S1-S2 protein construct confirmed the proposed model (Armstrong, Nature 395 (1998), 913-917. AMPA receptor subunits share an

approximately 70 % overall sequence homology, with over 90% identical sequences within the binding region S1/S2.

Although kainate receptors do not coassemble with AMPA receptors, they share substantial sequence homology as well as structural and functional similarities to AMPA-receptors. The sequence homology between GluR3 and GluR6 for example is app. 40%, and large portions of intra- and extracellular domains can be exchanged between receptors without loosing receptor function (Kuusinen, EMBO 24 (1995), 6327-6332; Stern-Bach, 1994, loc. cit.). Both AMPA- and kainate receptors show rapid and almost complete desensitization upon exposure of glutamate, yet they vary in their kinetics of recovery from desensitization and their specificity for blockers of desensitization such as cyclothiazide and concavalin A (Partin, 1993, loc. cit.).

In AMPA receptors desensitization is modulated by alternative splicing and RNA editing of segments in S2. The alternative spliced versions (known as 'flip' and 'flop') differ in their time course of desensitization and in their sensitivity to the desensitization blocker cyclothiazide (Sommer, Science 249 (1990), 1580-1585; Mosbacher, Science 266 (1994), 1059-1062; Partin, Mol. Pharmacol. 46 (1994), 129-138) and some of the molecular determinants for these differences have been elucidated (Partin, Neuron 14 (1995), 883-843; Partin, J. Neurosci. 16 (1996), 6634-6647). The amino acid preceding the alternative spliced 'flip' and 'flop' modules is subject to RNA editing and the edited channels possess faster recovery rates from desensitization (R/G site; Lomeli, Science 266 (1994), 1709-1713). Recently, it has been also demonstrated that residues at the N-terminus of S2 modulate desensitization of GluR1 (Mano, J.B.C. 271 (1996), 15266-15302) and GluR6 receptors (Swanson, Neuron 19 (1997), 913-926). Currently, it is not exactly clear how these sites participate in the desensitization process, and if, beside S2, structures in other parts of the protein are also involved. In NMDA receptors, for example, it been recently shown that structures flanking S1 control glycine-independent desensitization (Krupp, Neuron 20 (1998), 317-327; Villarroel, Neuron 20 (1998), 329-339).

Although both AMPA and kainate receptors desensitize upon continuous application of glutamate, specific kinetic parameters vary considerably. These include the time course for recovery from desensitization, the differential sensitivity to allosteric modulators and the shape and extent of desensitization produced by other agonists (reviewed in Bettler and Mulle, Neuropharmacology 34 (1995), 123-139).

Said desensitization of AMPA-receptors is thought to shape the synaptic response and to act as a neuroprotective mechanism at central synapses. However, very little is known about relevant structures and mechanisms underlying the gating process and the basic mechanism responsible for desensitization is poorly understood.

Interestingly, the most plausible theories of learning, pattern recognition and memory depend upon changes in the efficiency of chemical synapses. The glutamate receptor, especially the NMDA receptor, has attracted much attention in this context since its properties make it an ideal candidate for a receptor involved directly in the learning process. Additionally, the above described AMPA receptors play critical roles in learning and/or some forms of associative memory in animals (see, e.g., Tsien, Cell 87 (1996), 1327-1338) and there are suggestions that slowing AMPA receptor desensitization may have a cognitive enhancing effect (Ingvar, Exp. Neurology 146 (1997), 553-559). Furthermore, a large body of evidence indicates that glutamate receptors play a role in a number of brain diseases and the damage that occurs after head injury. It also has been known for decades that glutamate is toxic to neurons in culture and in vivo, and many experiments implicate the glutamate receptor as a mediator of these toxic effects of glutamate, (for review see, inter alia, Choi, Neuron 1 (1988), 623-624; Choi & Rothman, Annu. Rev. Neurol. 13 (1990), 171-182; Storey, Ann. Neurol. 32 (1992), 526-534; and Appel, Trends Neurosci. 16 (1993), 3-5). It is furthermore well known that glutamate (as well as aspartate) can be neurotoxic, especially when energy supply is compromised (reviewed, inter alia, in Dingledine, Pharmaco. Rev. 51 (1999), 7-61). These observations have led investigators to suggest that many

neurological accidents, including strokes in which there is a loss of oxygen and glucose or epileptic seizures, result in brain damage because of over-stimulation by glutamate. It has also been proposed that degenerative diseases such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) may involve neuronal cell death caused by excessive activation of the glutamate receptor system. Neurodegeneration associated with a variety of acute and chronic disorders (ischemic stroke, epilepsy, AIDS dementia, Rasmussen encephalitis among others) may, therefore, be caused in part by overactivation of glutamate receptors. Indeed, there is evidence from animal studies for marked neuroprotective effects of NMDA and AMPA receptor antagonists in models of ischemic stroke and epilepsy (Choi, Mt. Sinai J. Med. 65 (1998), 133-138).

The physiologically fast and complete desensitization of the above described wildtype AMPA receptors (time constant of 1 to 13 ms and inhibition of the current of 93 to 99% (Colquhoum, J. Physiol. 458 (1997), 261-28; Trussell, PNAS 85 (1988), 4562-4566; Mosbacher, Science 266 (1994), 1059-1062) is in vivo certainly neuroprotective for post-synaptic cells. However, the same physiological feature of fast desensitization makes experimental measurements of channel activities rather difficult and precludes the wildtype AMPA-receptors from a variety of pharmacological tests which may lead to a better understanding of the physiology of AMPA receptors and/or the detection/characterization of pharmacologically active substances capable of modifying said physiology.

Therefore, the technical problem underlying the present invention was to provide means and methods for the reproducible and reliable characterization of AMPA-receptor interactions with ligands and/or for the further elucidation of biochemical, biophysiological and/or electrophysiological properties of said receptors.

Accordingly, the present invention relates to a nucleic acid molecule encoding a (poly)peptide which has an amino acid sequence of a glutamate receptor of the

AMPA-type and/or of a subunit of said receptor and functions as a non-desensitizing AMPA-receptor or as a non-desensitizing subunit thereof, wherein the leucine corresponding to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ is replaced by an aromatic amino acid.

The term "nucleic acid molecule" in accordance with the present invention comprises coding and, wherever applicable, non-coding sequences (like promotors, enhancers etc.) In accordance with the present invention, the term " nucleic acid molecule" comprises also any feasible derivative of a nucleic acid to which a nucleic acid probe may hybridize. Said nucleic acid probe itself may be a derivative of a nucleic acid molecule capable of hybridizing to said nucleic acid molecule or said derivative thereof. The term " nucleic acid molecule" further comprises peptide nucleic acids (PNAs) containing DNA analogs with amide backbone linkages (Nielsen, Science 254 (1991), 1497-1500). The term "nucleic acid molecule" which encodes a (poly)peptide, in connection with the present invention, is defined either by (a) the specific nucleic acid sequences encoding the (poly)peptide specified in the present invention or (b) by nucleic acid sequences hybridizing under stringent conditions to the complementary strand of the nucleotide sequences of (a) and encoding a (poly)peptide deviating from the nucleic acid of (a) by one or more nucleotide substitutions, deletions, additions or inversions and wherein the nucleotide sequence shows at least 40%, preferably at least 50%, more preferably at least 60% identity with the nucleotide sequence of said encoded (poly)peptide having an amino acid sequence as defined herein above and functions as a non-desensitizing AMPA-receptor or as a non-desensitizing subunit thereof.

The term "(poly)peptide" means, in accordance with the present invention, a peptide, a protein, or a (poly)peptide which encompasses amino acid chains of a given length, wherein the amino acid residues are linked by covalent peptide bonds. However, peptidomimetics of such proteins/(poly)peptides wherein amino

acid(s) and/or peptide bond(s) have been replaced by functional analogs are also encompassed by the invention.

The term "non-desensitizing AMPA receptor", in accordance with this invention, denotes a glutamate receptor of the AMPA-type which does not desensitize in response to glutamate and/or its analogue(s) while other receptor channel properties remain intact. Since wildtype AMPA-glutamate receptors desensitize rapidly and almost completely in response to glutamate and/or its analogue(s), the term "non-desensitizing AMPA-receptor" also comprises, in accordance with this invention, AMPA receptors which desensitize slower and with less efficacy when compared to the corresponding wildtype glutamate receptor of the AMPA-type. In accordance with this invention, the term "AMPA-receptor" or "glutamate receptor of the AMPA-type" denotes any of the four AMPA-selective subunits, GluR1 to GluR4. Furthermore, said term denotes assembled structures forming distinct channels in heterooligomeric form and also comprises homooligomeric assemblies. Since AMPA receptor subunits only assemble with other AMPA receptor subunits but not with subunits from kainate – or NMDA receptors (Wenthold, J. Biol. Chem. 267 (1992), 501-507; Brose, J. Biol. Chem. 269 (1994), 16780-16784), the term "non-desensitizing AMPA receptor" also comprises the combination of at least one non-desensitizing AMPA receptor subunit with desensitizing (preferably wildtype) AMPA receptor subunits.

The term "leucine corresponding to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$" means, according to this invention, a specific leucine residue in a known wildtype sequence lying in a stretch of amino acid residues that form part of a glutamate binding site, wherein said glutamate binding side includes in the rat AMPA-receptor $GluR1_{flip}$, the leucine that lies between T494 and R499 (as shown in the appended examples). The wildtype rat AMPA receptor sequence of $GluR1_{flip}$ is well known in the art and, inter alia, shown in SEQ ID NO. 1 (see also GenEMBL accession number X17184 and Hollmann,

Nature 342 (1989), 643-648. Said leucine position 497 of the rat GluR1$_{flip}$ subunit, corresponds, inter alia, to the position 497 of the human GluR1 or the mouse GluR1 subunit. Said position 497 corresponds, however, in the rat GluR2, human GluR2 or mouse GluR2 to position 504 of the known AMPA-selective subunits. Furthermore, said position 497 of the rat AMPA-receptor GluR1$_{flip}$ corresponds to position 507 of the rat GluR3 subunit, to the position 505 of the rat GluR4 or the human GluR4 subunit, or to the position 513 of the human GluR3 subunit.

It was surprisingly found that the substitution/replacement of the leucine corresponding to position 497 of the wildtype rat AMPA-receptor GluR1$_{flip}$ (or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor GluR1$_{flip}$) with an aromatic amino acid results in a non-desensitizing receptor. However, corresponding reverse mutations in other glutamate receptors, for example Y521L in kainate receptor subunit GluR6, does not lead to a non-desensitizing receptor. Considering the known affinities of different AMPA receptor subunits for agonists, the person skilled in the art can easily employ the teachings of the present invention and deduce which subunit of an AMPA receptor should be modified in order to obtain a nondesensitizing AMPA receptor according to this invention. The different affinitites of AMPA receptors are well known in the art (see, inter alia, Mosbacher, Science 266 (1994), 1059-1062). Therefore, if an AMPA-receptor of higher affinity isdesired, the person skilled in the art might choose GluR1. In contrast, for AMPA-receptors of lower affinity, GluR3 or GluR4 may be employed.

The wildtype amino acid sequences of different glutamate receptors and/or their subunits are well-known in the art (see, inter alia, Hollmann, Ann. Rev. Neurosci. 17 (1994), 31-108) and easily obtainable from electronic databases (for examble, GenBANK or GenEMBL). For further wildtype sequences of AMPA-receptors and/or their subunits, for example from other species, that will be isolated in the future, due to the high homology of AMPA-receptors, the position correponding to L 497 of the rat GluR1 is easily deducible employing the sequence information

which is already available. Methods to be employed in order to elucidate further wildtype sequences of glutamate receptors of the AMPA-type and/or their subunits and methods to identify the leucine which corresponds to the leucine on position 497 of the rat GluR1$_{flip}$ subunit comprise, inter alia, standard homology screenings and PCR-mediated screening techniques for related sequences. For the identification of further wildtype sequences of glutamate receptors of the AMPA-type, as well as for the detection of the relevant amino acid residues corresponding to the leucine on position 497 of the rat GluR1$_{flip}$, computer programs may be utilized.

For example, BLAST2.0, which stands for Basic Local Alignment Search Tool (Altschul, Nucl. Acids Res. 25 (1997), 3389-3402; Altschul, J. Mol. Evol. 36 (1993), 290-300; Altschul, J. Mol. Biol. 215 (1990), 403-410), can be used to search for local sequence alignments. BLAST produces alignments of both nucleotide and amino acid sequences to determine sequence similarity. Because of the local nature of the alignments, BLAST is especially useful in determining exact matches or in identifying similar sequences. The fundamental unit of BLAST algorithm output is the High-scoring Segment Pair (HSP). An HSP consists of two sequence fragments of arbitrary but equal lengths whose alignment is locally maximal and for which the alignment score meets or exceeds a threshold or cutoff score set by the user. The BLAST approach is to look for HSPs between a query sequence and a database sequence, to evaluate the statistical significance of any matches found, and to report only those matches which satisfy the user-selected threshold of significance. The parameter E establishes the statistically significant threshold for reporting database sequence matches. E is interpreted as the upper bound of the expected frequency of chance occurrence of an HSP (or set of HSPs) within the context of the entire database search. Any database sequence whose match satisfies E is reported in the program output.

Analogous computer techniques using BLAST (Altschul, 1997, 1993 and 1990, supra) are used to search for identical or related molecules in nucleotide databases such as GenBank or EMBL. This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search

can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score which is defined as:

$$\frac{\%\text{sequence identity} \times \%\text{ maximum BLAST score}}{100}$$

and it takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1-2% error; and at 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The term "by comparison of homology" denotes, in accordance with this invention, that amino acid sequences of other glutamate receptors of the AMPA-types, or subunits thereof, are compared with the amino acid sequence of the amino acid sequences of the AMPA-receptor $GluR1_{flip}$ (as depicted, inter alia, in SEQ ID NO: 1). "Homology" is understood to refer in this context to a sequence identity of glutamate receptors of the AMPA-type of at least 60%, particularly of a amino acid sequence identity of 70%, preferably more than 80% and still more preferably more than 90% on the amino acid level. The present invention, however, comprises also (poly)peptides deviating from wildtype amino acid sequences of glutamate receptors of the AMPA-type described herein above, wherein said deviation may be, for example, the result of amino acid and/or nucleotide substitution(s), deletion(s), addition(s), insertion(s), duplication(s), inversion(s) and/or recombination(s) either alone or in combination. Those deviations may naturally occur or be produced via recombinant DNA techniques well known in the art; see, for example, the techniques described in Sambrook (Molecular Cloning; A Laboratory Manual, 2nd Edition, Cold Spring Harbour Laboratory Press, Cold Spring Harbour, NY (1989)) and Ausubel, "Current Protocols in Molecular Biology", Green Publishing Associates; and Wiley Interscience, N.Y. (1989). The allelic variations may be naturally occurring allelic variants as well as synthetically produced or genetically engineered variants. The (poly)peptides, peptides or protein fragments encoded by the various derivatives, allelic variants, homologues or analogues of the above-described nucleic acid molecules encoding non-

desensitizing AMPA-recptors and/or subunits thereof may share specific common characteristics, such as molecular weight, immunological reactivity, conformation etc., as well as physical properties, such as electrophoretic mobility, chromatographic behavior, sedimentation coefficients, pH optimum, stability, solubility, spectroscopic properties etc.

In a preferred embodiment, the nucleic acid molecule of the invention is (a) a nucleic acid molecule comprising a nucleic acid molecule encoding the (poly)peptide having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, or SEQ ID NO: 10, wherein the ieucine residue corresponding to position 497 of SEQ ID NO: 1, 5 or 9, corresponding to position 504 of SEQ ID NO: 2, 6 or 10, corresponding to position 507 of SEQ ID NO: 3, to position 505 of SEQ ID NO: 4 or 8, or corresponding to position 513 of SEQ ID NO: 7 is replaced by an aromatic amino acid; or (b) a nucleic acid molecule comprising a nucleic acid molecule encoding the (poly)peptide having the DNA sequence of SEQ ID NO: 11, SEQ ID NO. 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 18, SEQ ID NO: 20, wherein the codon represented by nnn corresponds to a codon coding for an aromatic amino acid; (c) a nucleic acid molecule hybridizing to the complementary strand of a nucleic acid molecule of (a) or (b); or the nucleic acid molecule of the invention is (d) a nucleic acid molecule being degenerate as a result of the genetic code to the nucleotide sequence of a nucleic acid molecule as defined in (c).

The term "codon represented by nnn corresponds to a codon coding for an aromatic amino acid" means, in accordance with the present invention, a codon which, according to the standard genetic code (as illustrated, inter alia, in Stryer (1995), "Biochemistry", Freemann and Compagny, ISBN 0-7167-2009-4) codes for any aromatic amino acid. For example, the codons TAT and TAC code for tyrosine, the codons TTT and TTC code for phenylalanine, the codon TGG codes for tryptophane, the codons CAT and CAC code for histidine.

The term "hybridizes" as used in accordance with the present invention may relate to hybridizations under stringent or non-stringent conditions. If not further specified, the conditions are preferably non-stringent. Said hybridization conditions may be established according to conventional protocols described, for example, in Sambrook, "Molecular Cloning, A Laboratory Manual", Cold Spring Harbor Laboratory, N.Y. (1989), Ausubel, "Current Protocols in Molecular Biology", Green Publishing Associates and Wiley Interscience, N.Y. (1989), or Higgins and Hames (Eds) "Nucleic acid hybridization, a practical approach" IRL Press Oxford, Washington DC, (1985). The setting of conditions is well within the skill of the artisan and can be determined according to protocols described in the art. Thus, the detection of only specifically hybridizing sequences will usually require stringent hybridization and washing conditions such as 0.1xSSC, 0.1% SDS at 65°. Non-stringent hybridization conditions for the detection of homologous or not exactly complementary sequences may be set at 6xSSC, 1% SDS at 65°C. As is well known, the length of the probe and the composition of the nucleic acid to be determined constitute further parameters of the hybridization conditions. Hybridizing nucleic acid molecules or molecules falling under alternative (c), supra, also comprise fragments of the molecules identified in (a), or (b) wherein the nucleotide sequence need not be identical to its counterpart in SEQ ID NOs: 11 to 20 said fragments representing nucleic acid sequences which code for non-desensitizing glutamate receptors of the AMPA-type or a functional fragment thereof, such as a (modified) glutamate binding side, and having a length of at least 12 nucleotides, preferably at least 15, more preferably at least 18, more preferably of at least 21 nucleotides, more preferably at least 30 nucleotides, even more preferably at least 40 nucleotides and most preferably at least 60 nucleotides. Furthermore, nucleic acid molecules which hybridize with any of the aforementioned nucleic acid molecules also include complemetary fragments, derivatives and allelic variants of these molecules. Functional fragments of non-desensitizing glutamate receptors of the AMPA-type and/or subunits may be comprised in a fusion and/or chimeric protein.

The term “derivative” means in this context that the nucleotide sequence of these nucleic acid molecules differs from the sequences of the above-described nucleic acid molecules in one or more nucleotide positions, that the nucleotide sequences are homologous (at least 40%, more preferably at least 50%. even more preferably 60%, most preferably at least 70%) at least to said nucleic acid molecules and that they comprise a codon replacing a codon coding for a corresponding amino acid residue to position 497 of the wildtype rat AMPA-receptor GluR1$_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor GluR1$_{flip}$, wherein said replacing codons code for any aromatic amino acid. Homology is understood to refer in the context of “fragments”, “derivatives” or “allelic variants” to a sequence identity of at least 60%, particularly an identity of at least 70%, preferably more than 80% and still more preferably more than 90%.

The nucleic acid molecule of the invention is a nucleic acid molecule encoding a (poly)peptide which comprises an aromatic amino acid at position 497 of SEQ ID NO: 1, 5 or 9, at position 504 of SEQ ID NO: 2, 6 or 10, at position 507 of SEQ ID NO: 3, at position 505 of SEQ ID NO: 4 or 8 or at position 513 of SEQ ID NO: 7, but differs therefrom by at least one mutation selected from the group consisting of amino acid substitutions, insertions, deletions, inversions and/or duplications.

Whereas nucleic acid molecules derived from a variety of species encoding homologous (poly)peptides representing glutamate receptors of the present invention are included in the present invention (for example, glutamate receptor genes have been reported in various species, like in insects, yeasts, fungi or plants (see, inter alia, Lam, Nature 396(1998), 125-126; Chiu, Molecular Biology and Evolution 16 (1999) 826-838)), in an even more preferred embodiment the nucleic acid molecule of the invention is derived from a rat, a mouse or a human.

Particularly preferred are nucleic acid molecule of the invention wherein said aromatic amino acid residue is tyrosine, phenylalanine, tryptophan or histidine.

In a preferred embodiment the nucleic acid molecule of the invention is DNA, RNA or PNA. The DNA may be cDNA, the RNA may be mRNA. Its origin may be natural, synthetic or semisynthetic or it may be a derivative, such as said peptide nucleic acid (Nielsen, Science 254 (1991), 1497-1500). Furthermore, said nucleic acid molecule may be a recombinantly produced chimeric nucleic acid molecule comprising any of the aforementioned nucleic acid molecules either alone or in combination.

In a particularly preferred embodiment, the nucleic acid molecule of the invention encodes a fusion protein. The term "fusion protein" denotes any polypeptide consisting or comprising of at least two (poly)peptides not naturally forming such a polypeptide. On the DNA level, the two or more coding sequences are fused in frame.

Such fusion proteins are, inter alia, exemplified in the append examples and comprise fusion proteins like specific chimeric polypeptides combining the glutamate binding domain of AMPA receptors with different parts of other glutamate receptors, like, kainate receptors (for example, GluR1-GluR6 or GluR3-GluR6 chimeras) , NMDA receptors and/or tACPD receptors. Chimeric exchanges between AMPA and kainate receptors represent conservative exchanges. as both receptors share high sequence homology. However, this invention also comprises fusion proteins wherein a part of or a complete AMPA receptor is linked to another protein or a part of another protein which does not function as a glutamate receptor. Examples of said other proteins comprise proteins representing further receptors, channels (voltage or transmitter gated) and/or pumps like, e.g. serotonin receptors, acetylcholine receptors, GABA receptors, glycine receptors, G-protein-coupled receptors and/or parts of these receptors. Additionally, said fusion protein may comprise proteins and/or parts which do not naturally function as receptors, channels and/or pumps. Therefore, the nucleic acid molecule of the present invention may also have the coding sequence fused in frame to, e.g. a sequence encoding a marker which allows, inter alia, the purification, isolation, and/or detection of the (poly)peptide of the present invention. Such a marker may be a label or a tag, like, e.g. GST, cellulose binding domain, green fluorescent protein,

maltose binding protein, alkaline phosphatase, lacZ, c-myc, His-tag, FLAG, EpiTag™, V5 tag, T7 tag, Xpress™ tag or Strep-tag. In accordance with the invention, two or more tags may be comprised by the fusion protein. Any additional domain present in the fusion protein of the present invention comprising a (poly)peptide as defined herein above according to this invention may be joined directly (i.e. no intervening amino acids) or may be linked via a (flexible) linker, advantageously a polypeptide linker. The above defined fusion protein may further comprise a cleavable linker or a cleavage site, which, for example, is specifically recognized and cleaved by proteinases or chemical agents. Cleavable linker sequences include, but are not limited to, Factor XA or enterokinase (Invitrogen, San Diego, USA).

Preferably, the nucleic acid molecule of the present invention is part of a vector. Therefore, the present invention relates in another embodiment to a vector comprising the nucleic acid molecule of this invention. Such a vector may be, e.g., a plasmid, cosmid, virus, bacteriophage or another vector used e.g. conventionally in genetic engineering, and may comprise further genes such as marker genes which allow for the selection of said vector in a suitable host cell and under suitable conditions.

Furthermore, the vectors may, in addition to the nucleic acid sequences of the invention, comprise expression control elements, allowing proper expression of the coding regions in suitable hosts. Such control elements are known to the artisan and may include a promoter, translation initiation codon, translation and insertion site for introducing an insert into the vector. Preferably, the nucleic acid molecule of the invention is operatively linked to said expression control sequences allowing expression in eukaryotic or prokaryotic cells. Particularly preferred are in this context control sequences which allow for correct expression in neuronal cells and/or cells derived from nervous tissue.

Control elements ensuring expression in eukaryotic and prokaryotic cells are well known to those skilled in the art. As mentioned above, they usually comprise regulatory sequences ensuring initiation of transcription and optionally poly-A

signals ensuring termination of transcription and stabilization of the transcript. Additional regulatory elements may include transcriptional as well as translational enhancers, and/or naturally-associated or heterologous promoter regions. Possible regulatory elements permitting expression in for example mammalian host cells comprise the CMV- HSV thymiakine kinase promoter, SV40, RSV-promoter (Rous sarcome virus), human elongation factor 1α-promoter, CMV enhancer, CaM-kinase promoter or SV40-enhancer. For the expression for example in nervous tissue and/or cells derived therefrom, several regulatory sequences are well known in the art, like the minimal promoter sequence of human neurofilament L (Charron, J. Biol. Chem 270 (1995), 25739-25745). For the expression in prokaryotic cells, a multitude of promoters including, for example, the tac-lac-promoter or the trp promoter, has been described. Beside elements which are responsible for the initiation of transcription such regulatory elements may also comprise transcription termination signals, such as SV40-poly-A site or the tk-poly-A site, downstream of the polynucleotide. In this context, suitable expression vectors are known in the art such as Okayama-Berg cDNA expression vector pcDV1 (Pharmacia), pRc/CMV, pcDNA1, pcDNA3 (In-Vitrogene, as used, inter alia in the appended examples), pSPORT1 (GIBCO BRL) or pGEMHE (Promega), or prokaryotic expression vectors, such as lambda gt11. Beside the nucleic acid molecules of the present invention, the vector may further comprise nucleic acid sequences encoding for secretion signals. Such sequences are well known to the person skilled in the art. Furthermore, depending on the expression system used leader sequences capable of directing the protein/(poly)peptide to a cellular compartment may be added to the coding sequence of the nucleic acid molecules of the invention and are well known in the art. The leader sequence(s) is (are) assembled in appropriate phase with translation, initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein, or a part thereof, into, inter alia, the extracellular membrane. Optionally, the heterologous sequence can encode a fusion protein including an C- or N-terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product. Once the vector has been incorporated into the appropriate host, the host is maintained under conditions

suitable for high level expression of the nucleotide sequences, and, as desired, the collection and purification of the proteins, antigenic fragments or fusion proteins of the invention may follow. Of course, the vector can also comprise regulatory regions from pathogenic organisms.

Furthermore, said vector may also be, besides an expression vector, a gene transfer and/or gene targeting vector. Gene therapy, which is based on introducing therapeutic genes (for example for vaccination) into cells by ex-vivo or in-vivo techniques is one of the most important applications of gene transfer. Suitable vectors, vector systems and methods for in-vitro or in-vivo gene therapy are described in the literature and are known to the person skilled in the art; see, e.g., Giordano, Nature Medicine 2 (1996), 534-539; Schaper, Circ. Res. 79 (1996), 911-919; Anderson, Science 256 (1992), 808-813, Isner, Lancet 348 (1996), 370-374; Muhlhauser, Circ. Res. 77 (1995), 1077-1086; Wang, Nature Medicine 2 (1996), 714-716; WO 94/29469; WO 97/00957, Schaper, Current Opinion in Biotechnology 7 (1996), 635-640 or Verma, Nature 389 (1997), 239-242 and references cited therein.

The nucleic acid molecules of the invention and vectors as described herein above may be designed for direct introduction or for introduction via liposomes, or viral vectors (e.g. adenoviral, retroviral) into the cell. Additionally, baculoviral systems or systems based on vaccinia virus or Semliki Forest Virus can be used as eukaryotic expression system for the nucleic acid molecules of the invention. In addition to recombinant production, fragments of the protein, the fusion protein or antigenic fragments of the invention may be produced by direct peptide synthesis using solid-phase techniques (cf Stewart et al. (1969) Solid Phase Peptide Synthesis, WH Freeman Co, San Francisco; Merrifield, J. Am. Chem. Soc. 85 (1963), 2149-2154). *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer, Foster City CA) in accordance with the instructions provided by the manufacturer. Various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

The present invention in addition relates to a host transformed with a vector of the present invention or to a host comprising the nucleic acid molecule of this invention. Said host may be any prokaryotic or eukaryotic cell. Suitable prokaryotic/bacterial cells are those generally used for cloning like E. coli or Bacillus subtilis. Said eukaryotic host may be a mammalian cell, an amphibian cell, an insect cell, a fungal cell, or a plant cell. Suitable fungal cells are yeast cells, preferably those of the genus Saccharomyces and most preferably those of the species S. cerevisiae. In a particularly preferred embodiment said mammalian cell is a neuronal cell and/or a cultured cell like, inter alia, a HEK 293 (human embryonic kidney) cell, a CHO, HeLa, NIH3T3, BHK or a PC12 cell. Said amphibian cell may be an oocyte. Said oocyte may be, inter alia, a frog oocyte, for example Xenopus laevis oocyte.

In a more preferred embodiment , the present invention relates to an host of the invention which is a non-human transgenic organism. Said non-human organism may be a mammal, anamphibian, an insect, a fungus or a plant. Particularly preferred non-human transgenic animals are Drosophila, C. elegans, Xenopus, mice and rats. Transgenic plants comprise, but are not limited to, wheat, tobacco, parsley and Arabidopsis. Transgenic fungi are also well known in the art and comprise, inter alia, yeasts, like S. pombe or S. cerevisae, or Aspergillus species.

In another embodiment, the present invention relates to a method for producing the (poly)peptide encoded by a nucleic acid molecule of the invention comprising culturing/raising the host of the invention and isolating the produced (poly)peptide.

A large number of suitable methods exist in the art to produce proteins/(poly)peptides in appropriate hosts. If the host is a unicellular organism or a mammalian or insect cell, the person skilled in the art can revert to a variety of culture conditions that can be further optimized without an undue burden of work. Conveniently, the produced protein is harvested from the culture medium

or from isolated (biological) membranes by established techniques. Furthermore, the produced protein/(poly)peptide may be directly isolated from the host cell. Said host cell may be part of or derived from a part of a host organism, for example said host cell may be part of the CNS of an animal or the harvestable part of a plant. Additionally, the produced (poly)peptide may be isolated from fluids derived from said host, like blood, milk or cerebrospinal fluid.

Additionally the present invention relates to a (poly)peptide that is encoded by the nucleic acid molecule of the invention or produced by the method of the invention. The (poly)peptide of the invention may accordingly be produced by microbiological methods or by transgenic mammals. It is also envisaged that the polypeptide of the invention is recovered from transgenic plants. Alternatively, the polypeptide of the invention may be produced synthetically or semi-synthetically.

In a further embodiment, the present invention relates to an antibody specifically directed to the (poly)peptide and/or fusion protein of the invention, wherein said antibody specifically reacts with an epitope comprising the aromatic amino acid which replaces the leucine at position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of said wildtype rat AMPA receptor $GluR1_{flip}$. Whether said antibody specifically reacts as defined herein above can easily be tested, inter alia, by comparing the reaction of said antibody with a wildtype AMPA-receptor (or a subunit or a fragment thereof) with the reaction of said antibody with a (poly)peptide of this invention.

The antibody of the present invention can be, for example, polyclonal or monoclonal antibodies. Techniques for the production of antibodies are well known in the are and described, e.g. in Harlow and Lane "Antibodies, A Laboratory Manual", CSH Press, Cold Spring Harbor, 1988. These antibodies can be used, for example, for the immunoprecipitation and immunolocalization of the (poly)peptides of the invention as well as for the monitoring of the presence of such

(poly)peptides, for example, in recombinant organisms, and for the identification of compounds interacting with the proteins according to the invention (as mentioned herein below). For example, surface plasmon resonance as employed in the BIAcore system can be used to increase the efficiency of phage antibodies which bind to an epitope of the polypeptide of the invention (Schier, Human Antibodies Hybridomas 7 (1996), 97-105; Malmborg, J. Immunol. Methods 183 (1995), 7-13). The present invention furthermore includes chimeric, single chain and humanized antibodies, as well as antibody fragments, like, inter alia, Fab fragments. Antibody fragments or derivatives further comprise $F(ab')_2$, Fv or scFv fragments; see, for example, Harlow and Lane, loc.cit.. Various procedures are known in the art and may be used for the production of such antibodies and/or fragments. Thus, the (antibody) derivatives can be produced by peptidomimetics. Further, techniques described for the production of single chain antibodies (see, inter alia, US Patent 4,946,778) can be adapted to produce single chain antibodies to polypeptide(s) of this invention. Also, transgenic animals may be used to express humanized antibodies to polypeptides of this invention. Most preferably, the antibody of this invention is a monoclonal antibody. The general methodology for producing, monoclonal antibodies is well-known and has been described in, for example, Köhler and Milstein, Nature 256 (1975), 494-496 and reviewed in J.G.R. Hurrel, ed., "Monoclonal Hybridoma Antibodies: Techniques and Applications", CRC Press Inc., Boco Raron, FL (1982), as well as that taught by L. T. Mimms et al., Virology 176 (1990), 604-619.

In yet another embodiment, the present invention relates to composition comprising the nucleic acid molecule, the (poly)peptide and/or the antibody of the invention.

The term “composition”, as used in accordance with the present invention, comprises at least one nucleic acid molecule, (poly)peptide, an antigenic and preferably immunogenic fragment of said (poly)peptide comprising an epitope comprising the aromatic amino acid which replaces the leucine at position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which

corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of said wildtype rat AMPA receptor $GluR1_{flip}$., a fusion protein, and/or an antibody of this invention and, optionally, further molecules, either alone or in combination, like e.g. molecules which are capable of suppressing glutamate release, capable of blocking, modulating and/or activating glutamate receptors or molecules which have neuroprotective and/or nootropic properties.

The composition may be in solid, liquid or gaseous form and may be, inter alia, in the form of (a) powder(s), (a) tablet(s), (a) solution(s) or (an) aerosol(s).

Furthermore, the present invention relates to a the composition of this invention which is a pharmaceutical composition, optionally further comprising an acceptable carrier and/or diluent and/or excipient. The pharmaceutical composition of the present invention may be particularly useful in preventing and/or treating pathological disorders in humans or animals. Said pathological disorders comprise, but are not limited to, neurological, neurodegenerative and/or neuro-psychiatric disorders. These disorders comprise, inter alia, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (FALS/SALS), ischemia, stroke, epilepsy, AIDS dementia and learning disorders. The pharmaceutical composition may also be used for prophylactic purposes.
Examples of suitable pharmaceutical carriers are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Compositions comprising such carriers can be formulated by well known conventional methods. These pharmaceutical compositions can be administered to the subject at a suitable dose. Administration of the suitable compositions may be effected by different ways, e.g., by intravenous, intraperitoneal, subcutaneous, intramuscular, topical, intradermal, intranasal or intrabronchial administration. However, it is also encisaged that the pharmaceutical compostions are directly applied to the nervous tissue. The dosage regimen will be determined by the

attending physician and clinical factors. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, general health, age, sex, the particular compound to be administered, time and route of administration, and other drugs being administered concurrently. Pharmaceutically active matter may be present, inter alia, in amounts between 1 ng and 100 mg per dose; however, doses below or above this exemplary range are envisioned, especially considering the aforementioned factors. If the regimen is a continuous infusion, it should also be in the range of 1 µg to 10 mg units per kilogram of body weight per minute, respectively. Progress can be monitored by periodic assessment. The compositions of the invention may be administered locally or systemically. Administration will generally be parenterally, e.g., intravenously. The compositions of the invention may also be administered directly to the target site, e.g., by biolistic delivery to an internal or external target site or by catheter to a site in an artery. Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. Furthermore, the pharmaceutical composition of the invention may comprise further agents, depending on the intended use of the pharmaceutical composition. Such agents may be drugs acting on the central nervous system as well as on small, unmyelinated sensory nerve terminals (like in the skin), neurons of the peripheral nervous system of the digestive tract. Furthermore said pharmaceutical composition may additionally comprise drugs and compounds which may influence glutamate-uptake or enhanced glutamate release, leading

to excessive activation of the glutamate receptor system, like, inter alia, AMPAkines (Ingvar (1997), loc. cit.). Further drugs acting on the central nervous system comprise, but are not limited to, antidepressants (like monoamine oxidase inhibitors, such as phenelzine) anti-seizure drugs (like, e.g., carbomazepine, phenobarbital or valproate), anti-stroke drugs (like, e.g. water-soluble AMPA receptor antagonists as described, inter alia, in Small, Neuroreport 9 (1998), 1287-1290 or in Turski, Proc. Natl. Acad. Sci. USA 95 (1998), 10960-10965) or drugs employed in the alleviation of learning disorders or for cognitive enhancement, like, inter alia, AMPAkines (Ingvar (1997), loc. cit.).

Additionally, in accordance with this invention, the composition of this invention may be a diagnostic composition, optionally further comprising suitable means for detection. The diagnostic composition comprises at least one of the aforementioned compounds of the invention. The diagnostic composition may be used, inter alia, for methods for determining the expression of the nucleic acids and/or polypeptides of the invention by detecting, inter alia, the presence of the corresponding mRNA which comprises isolation of RNA form a cell, contacting the RNA so obtained with a nucleic acid probe as described above under hybridizing conditions, and detecting the presence of mRNAs hybridized to the probe. Furthermore, (poly)peptides of the invention can be detected with methods known in the art , which comprise, inter alia, immunological methods, like, ELISA or Western blotting.

Furthermore, the diagnostic composition of the invention may be useful, inter alia, in detecting the prevalence, the onset or the progress of a disease related to the aberant expression of a polypeptide of the invention. Accordingly, the diagnostic composition of the invention may be used, inter alia, for assessing the prevalence, the onset and/or the disease status of neurological, neurodegenerative and/or neuro-psychiatric disorders, as defined herein above. It is also contemplated that antibodies and compositions comprising such antibodies of the invention may be useful in discriminating (the) stage(s) of a disease.

The diagnostic composition optionally comprises suitable means for detection. The nucleic acid molecule(s), vector(s), host(s), antibody(ies), (poly)peptide(s), fusion protein(s) described above are, for example, suitable for use in immunoassays in which they can be utilized in liquid phase or bound to a solid phase carrier. Examples of well-known carriers include glass, polystyrene, polyvinyl chloride, polypropylene, polyethylene, polycarbonate, dextran, nylon, amyloses, natural and modified celluloses, polyacrylamides, agaroses, and magnetite. The nature of the carrier can be either soluble or insoluble for the purposes of the invention.
Solid phase carriers are known to those in the art and may comprise polystyrene beads, latex beads, magnetic beads, colloid metal particles, glass and/or silicon chips and surfaces, nitrocellulose strips, membranes, sheets, duracytes and the walls of wells of a reaction tray, plastic tubes or other test tubes. Suitable methods of immobilizing nucleic acid molecule(s), vector(s), host(s), antibody(ies), (poly)peptide(s), fusion protein(s) etc. on solid phases include but are not limited to ionic, hydrophobic, covalent interactions and the like. Examples of immunoassays which can utilize said compounds of the invention are competitive and non-competitive immunoassays in either a direct or indirect format. Commonly used detection assays can comprise radioisotopic or non-radioisotopic methods. Examples of such immunoassays are the radioimmunoassay (RIA), the sandwich (immunometric assay) and the Northern or Southern blot assay. Furthermore, these detection methods comprise, inter alia, IRMA (Immune Radioimmunometric Assay), EIA (Enzyme Immuno Assay), ELISA (Enzyme Linked Immuno Assay), FIA (Fluorescent Immuno Assay), and CLIA (Chemioluminescent Immune Assay). Furthermore, the diagnostic compounds of the present invention may be are employed in techniques like FRET (Fluorescence Resonance Energy Transfer) assays.

Appropriate labels and methods for labeling are known to those of ordinary skill in the art. Examples of the types of labels which can be used in the present invention include inter alia, fluorochromes (like fluorescein, rhodamine, Texas Red, etc.), enzymes (like horse radish peroxidase, β-galactosidase, alkaline phosphatase),

radioactive isotopes (like ^{32}P or ^{125}I), biotin, digoxygenin, colloidal metals, chemi- or bioluminescent compounds (like dioxetanes, luminol or acridiniums).

A variety of techniques are available for labeling biomolecules, are well known to the person skilled in the art and are considered to be within the scope of the present invention and comprise, inter alia, covalent coupling of enzymes or biotinyl groups, phosphorylations, biotinylations, random priming, nick-translations, tailing (using terminal transferases). Such techniques are, e.g., described in Tijssen, "Practice and theory of enzyme immuno assays", Burden and von Knippenburg (Eds), Volume 15 (1985); "Basic methods in molecular biology", Davis LG, Dibmer MD, Battey Elsevier (1990); Mayer, (Eds) "Immunochemical methods in cell and molecular biology" Academic Press, London (1987); or in the series "Methods in Enzymology", Academic Press, Inc.

Detection methods comprise, but are not limited to, autoradiography, fluorescence microscopy, direct and indirect enzymatic reactions, etc.

Said diagnostic composition may be used for methods for detecting the abundance of a nucleic acid molecule of the invention in a biological and/or medical sample and/or for detecting expression of a nucleic acid molecule (i.e. an expressed (poly)peptide) of the invention. Furthermore, said diagnostic composition may also be used in methods of the present invention, inter alia, for the detection of specific antagonists or agonists for glutamate receptors (see herein below).

In yet another embodiment, the present invention relates to a method for the blocking of desensitization of a glutamate receptor of the AMPA-type, comprising the step of replacing a leucine corresponding to position 497 of the wildtype rat AMPA-receptor GluR1 or corresponding by comparison of homology to position 497 of the rat AMPA-receptor GluR1 by an aromatic amino acid. Said leucine might be replaced, inter alia, by recombinant methods known in the art and exemplified in the appended examples.

Furthermore, the present invention relates to a method for identifying molecules which are capable of interacting with glutamate receptors of the AMPA-type, comprising the steps of (a) contacting a non-desensitizing AMPA-receptor as encoded by a nucleic acid molecule, a vector, a host, or an antibody of this invention with said molecule; and (b) identifying among these molecules the molecules which are capable of interacting with said glutamate receptor of the AMPA-type. In case of the nuclaic acid molecule and7or the vector of this invention, said nucleic acid molecuel and/or vector may be first activated and/or expressed

Additionally, the present invention relates to a method for the characterization of molecules which are capable of interaction with glutamate receptors of the AMPA-type, comprising the steps of (a) contacting a non-desensitizing AMPA-receptor as defined herein above or a vector, a host, or an antibody of this invention with said molecules; and (b) measuring and/or detecting the characteristic effect said molecules evoke.
Said identification and/or characterization of molecules which are capable of interacting with glutamate receptors of the AMPA-type, may be, inter alia, achieved by transfecting an appropriate host with a nucleic acid molecule of invention. Said hosts comprise, but are not limited to, HEK 293 cells or frog oocytes. After expression of a non-desensitizing AMPA-receptor, membrane currents may be deduced in the absence and/or presence of the molecule to be identified and/or characterized. Methods for the deduction of membrane currents are well known in the art and comprise, e.g., patch clamp methods as described in Hamill, Pfluger's Arch. 391 (1981), 85-100 or two-electrode voltage clamp in oocytes, as described in Methfessel, Pflügers Archive 407 (1986) 577-588.

Furthermore, the present invention relates to a method of screening for molecules which are capable of interacting with glutamate receptors of the AMPA-type, comprising the steps of (a) contacting a non-desensitizing AMPA-receptor as encoded by a nucleic acid molecule, a vector, a host of the invention with a candidate molecule; and (b) measuring and/or detecting a response; and

(c) comparing said response to a standard response as measured in the absence of said candidate molecule.

Potential candidate molecules or candidate mixtures of molecules may be, inter alia, substances, compounds or compositions which are of chemical or biological origin, which are naturally occurring and/or which are synthetically, recombinantly and/or chemically produced. Thus, candidate molecules may be proteins, protein-fragments, peptides, amino acids and/or derivatives thereof or other compounds, such as ions, which bind to and/or interact with wild-type AMPA-receptors. Such binding and/or interacting candidate compounds may be found employing, inter alia, yeast two-hybrid systems or modified yeast two-hybrid systems as described, for example, in Fields, Nature 340 (1989), 245-246; Gyuris, Cell 75 (1993), 791-801; or Zervos, Cell 72 (1993), 223-232.

Furthermore, potential candidate molecules may be contacted with a cell, such as an oocyte or a HEK 293 cell, which expresses a (poly)peptide of the invention or with a membrane patch comprising a (poly)peptide of the invention and a corresponding response (inter alia, a dose-response response, a current-response, or single current channel response) may be measured in order to elucidate any effect said candidate molecule causes.

Within the scope of the present invention are also methods for identifying, characterizing and for screening of molecules which are capable of interacting with glutamate receptors of the AMPA-type which comprise so-called high-throughput screening methods and similar approaches which are known in the art (Spencer, Biotechnol. Bioeng. 61 (1998), 61-67; Oldenburg, Annu. Rep. Med. Chem. 33 (1998), 301-311) carried out using 96-well, 384-well, 1536-well (and other) commercially available plates. Further methods to be employed in accordance with the present invention comprise, but are not limited to, homogenous fluorescence readouts in high-throughput screenings (as described, inter alia, in Pope, Drug Discovery Today 4 (1999), 350-362). The method of the present invention for identification, characterization and/or

screening of molecules capable of interacting with glutamate receptors of the AMPA-type can, inter alia, employ hosts as defined herein which express the (poly)peptide of the present invention. Cell-based assays, instrumentation for said assays and/or measurements are well-known in the art and described, inter alia, in Gonzalez, Drug Discovery Today 4 (1999), 431-439 or Ramm, Drug Discovery Today 4 (1999), 401-410. For example, the coupling of an receptor activity to changes in intracellular Ca^{2+} is a general and powerful method for high throughput drug screening. Quantitative changes in intracellular calcium concentration can be detected by imaging techniques using Ca^{2+} sensitive dyes such as FURA II and their membrane permeable chemical analogs (Tsien, Biochemistry 19 (1980), 2396-2404; Grynkiewicz, Biological Chemistry 260 (1985), 3440-3450). Since homomeric AMPA receptors of the genes 1,3 and 4 are Calcium-permeable (Burnashev, Neuron 8 (1992) 189-198), cells, cell lines and hosts, expressing a (poly)peptide of this invention, i.e. a non-desensitizing version of an AMPA-receptor, such as the rat GluRI-mutant L497Y descibed in the appended examples, will show an increase of intracellular calcium concentration, depending on degree of glutamate receptor stimulation. Thus, the agonist and antagonist potency of a candidate molecule for AMPA-receptors is detectable using the (poly)peptide of the invention and/or employing the aforementioned receptors of the invention expressed in cell cultures.

Additionally, the present invention relates to a method for the production of a pharmaceutical composition comprising the steps of the method of the invention for identifying, characterizing and/or screening of molecules which are capable of interacting with glutamatic receptors of the AMPA-type and further comprising a step, wherein a derivative of said identified, characterized and/or screened molecule is generated. Such a derivative may be generated by, inter alia, peptidomimetics.

The invention furthermore relates to a method for the production of a pharmaceutical composition comprising the steps of the method of the invention for identifying, characterizing, screening and/or derivatizing of molecules which

are capable of interacting with glutamatic receptors of the AMPA-type and formulating the molecules identified, characterized, screened and/or derivatized in pharmaceutically acceptable form.

In a more preferred embodiment the present invention relates to a method wherein said molecule(s) are neuroprotective and/or (a) nootropic molecule(s).

In a yet more preferred embodiment the present invention relates to a method wherein said molecule(s) are antagonist(s), partial antagonist(s), partial agonist(s) and/or agonist(s) for glutamate receptors. Known agonists for AMPA-receptors comprise L-glutamate, quisqualate, (RS)-alpha-amino-3-hydroxy-5-methyl—4-isoxazoleepropionic acid (AMPA) or kainate (partial agonist); whereas known antagonsits are, inter alia, kynurate, 6-nitro-7-sulphamoyl-benzo(F)quinoxalinedion (NBQX) or l-glutamic acid diethyl ester (noncompetitive antagonist).

In accordance with the present invention, the term "antagonist" denotes molecules/substances, which are capable of inhibiting and/or reducing an agonisitic effect. The term "antagonist" comprises competitive, non-competitive , functional and chemical antagonists as described, inter alia, in Mutschler, "Arzneimittelwirkungen" (1986), Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Germany. The term "partial antagonist" in accordance with the present invention means a molecule/substance that is capable of incompletely blocking the action of agonists through, inter alia, a non-competitive mechanism. As "agonist", in accordance with this invention, molecules/substances are denoted which have an affinity as well as an intrinsic activity. Mostly, said intrinsic activity (α) is defined as being proportional to the quotient of the effect, triggered by said agonist (E_A) and the effect which can be maximally obtained in a given biological system (E_{max}): therefore, the intrinsic activity can be defined as

$$\alpha \sim \frac{E_A}{E_{\max}}$$

The highest relative intrinsic activity results from $E_A/E_{max}=1$. Agonists with an intrinsic activity of 1 are full agonists, whereas substances/molecules with an intrinsic activity of >0 and <1 are partial agonists. Partial agonists show a dualistic effect, i.e. they comprise agonistic as well as antagonistic effects.

The person skilled in the art can, therefore, easily employ the compounds and the methods of this invention in order to elucidate the agonistic and/or antagonistic effects and/or characteristics of a compound/molecule/substance to be identified and/or characterized in accordance with any of the above descibed methods.

The invention also relates to the use of a non-desensitizing AMPA-receptor as encoded by the nucleic acid molecule of the invention or the use of a host of the invention as a biosensor for glutamate concentrations. For example, a patch or cell in whole-cell configuration (sniffer) expressing a (poly)peptide, i.e. a nondesensitizing receptor, of the present invention can first be calibrated by briefly exposing it to saturating agonist concentration via external perfusion to determine the maximal current of the sniffer. Subsequently, the patch or cell is placed into a sample, tissue or specimen. In the presence of, for example, L-glutamate in the solution, a current should be produced by binding of glutamate to the receptors that in turn causes the opening of the channels. Since the developing current will follow strict dependency on the glutamate occupancy on the patch, the concentration of glutamate in the sample can be easily determined by comparing the fraction of the maximal current and the current induced by the specimen. These "sniffer patch" methods are well-known in the art and described, inter alia, in Hume, Nature 305 (1983), 632-634. The well defined dose-response curve for glutamate on the nondesensitizing receptor (as illustrated in the appended examples) allows then a reconstruction of the glutamate concentration. Ligand–gated ion channel receptors have been used to determine the identitiy of neurotransmitters in a qualitative manner (Copenhagen, (1989) Nature 341, 536-539; Allen, (1997) Trends Neurosci. 5, 192-197), however, the above mentioned technique furthermore allows the

quantitative determination of glutamate concentration of an aqueous sample, whether it is of biological origin or not.

Furthermore, the present invention relates to the use of a non-desensitizing AMPA-receptor as encoded by the nucleic acid molecule of the invention or use of a host as defined herein above for the characterization of glutamate receptor channel properties. For example, by studying the single channel properties of non-desensitizing AMPA-receptors (like, inter alia, the GluR1-GluR6 and GluR3-GluR6 chimeras of the appended examples), it is possible to detect conductance states depending on the number of bound agonists or antagonists. The methods for such characterizations are well known in the art and comprise methods such as patch clamp. Techniques and methods for glutamate receptor property measurements are also described in Jahr, Nature 325 (1987), 522-525 or Swanson, J. Neurosci. 17 (1997), 58-69.

The invention further relates to the use of the nucleic acid molecule, of the vector, the host, the (poly)peptide and/or the antibody of the invention for the preparation of a pharmaceutical composition for preventing and/or treating neurological and/or neurodegenerative disorders.

In a preferred embodiment said neurological and/or neurodegenerative disorders are selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (FALS/SALS), ischemia, stroke, epilepsy, AIDS dementia and learning disorders.

In another embodiment the present invention relates to the use of the nucleic acid molecule, the vector and/or the host cell of the invention in gene therapy. For example, the nucleic acid molecules of the present invention could be expressed in tissues with pathologically low synaptic activity either due to breakdown of tissue (stroke, eplilepsy, postraumatic degeneration, ALS, Alzheimer) or through traumaticcally induced removal of input fibers (spinal cord

injury). Furthermore, said nucleic acid molecules could be expressed in patients suffering from learning disorders.

Additionally, the present invention relates to a kit comprising the nucleic acid molecule, the vector, the host, the (poly)peptid, or the antibody of the invention or the molecule as identified or characterized in a method of the present invention.

Advantageously, the kit of the present invention further comprises, optionally (a) reaction buffer(s), storage solutions and/or remaining reagents or materials required for the conduct of scientific or diagnostic assays or the like. Furthermore, parts of the kit of the invention can be packaged individually in vials or bottles or in combination in containers or multicontainer units.

The kit of the present invention may be advantageously used, inter alia, for carrying out the method of producing a (poly)peptide of the invention, the method(s) of identification and/or characterization of molecules specifically interacting with glutamate receptors as descibed herein above and/or it could be employed in a variety of applications referred herein, e.g., as diagnostic kits, as research tools or therapeutic tools. Additionally, the kit of the invention may contain means for detection suitable for scientific, medical and/or diagnostic purposes. The manufacture of the kits follows preferably standard procedures which are known to the person skilled in the art. Furthermore, the kit of the present invention may be used for the preparation of biosensors for glutamate concentrations.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integer or step.

The figures show:

Figure 1: Desensitization properties of GluRI receptors

(A) Typical response to an application of 10 mM L-glutamate (1s duration, indicated with black bar) to an outside-out membrane patch obtained from a HEK293 cell transiently transfected with the GluR1 wildtype receptor. A rapidly desensitizing inward current is induced, that is only observable by application with a rapid perfusion system. The drawing above the current trace schematizes the primary amino acid structure of a single AMPA receptor subunit, with the putative transmembrane region indicated as thickening of the bar.

(B) Typical response to an application of 10 mM L-glutamate (1s duration, indicated with black bar) to an outside-out membrane patch obtained from a HEK293 cell transiently transfected with the GluR1 receptor with the point mutation Leucine to Tyrosine at position 497 (see SEQ ID NO: 1). During the entire period of agonist application, the agonist induced current is maintained in its activity. The white line within the first segment of the drawing schematizes the position of the point mutation.

(C) The current trace shows whole cell recordings from a cell transfected with GluR1 L497Y during application of various concentrations of the agonist l-glutamate. The concentrations and the application periods of the solutions containing specific agonist concentrations are indicated as numbers above the black bars (in μMol). The solution exchange under whole cell recordings are app. 20 fold slower, but allow due to the nondesensitizing phenotype an accurate measure for the agonist efficacy and affinity.

(D) The graph shows the dose- response relationship from 11 whole-cell recordings such as shown as an example in Fig. 1C for the agonists L-glutamate and Quisqualate. Error bars indicate standard error and are extremely small, thus allowing accurate determination of affinity and efficacy with few experiments.

Figure 2: The role of the N-terminal region in AMPA-type glutamate receptor desensitization.

(A-D) Responses to rapid application of 10 mM glutamate from outside-out patches expressing homomeric receptors GluR3$_{flip}$ (A), GluR6$_{R}$ (B), R6TM1R3$_{flip}$ (C), and R3(R6S1)$_{flip}$ (D) measured at -60 mV. The subunit type is illustrated above each trace. Black bars correspond to GluR3, white bars to GluR6. The small three vertical bars correspond to the transmembrane domains M1, M3 and M4 respectively. The numbers correspond to the first, beginning of M1 and last amino acid, respectively (panels A-C) and those at the S1 junction (panel D). The amino acid numbering starts from the first methionine of the open reading frame. All responses are averaged from 2-50 episodes. Inset in panel A shows the same response on a 50 fold faster time scale. The solution exchange was estimated by the open tip current at the end of each experiment (as shown above inset).

(E) Current/voltage relationship of R3(R6S1)$_{flip}$ in outside-out patch configuration. Voltage was ramped from -80 to +20 mV at 1mV/ms. The trace represents an average of 7 episodes in the presence of 10 mM glutamate after leak subtraction. Patch solutions contained no polyamines.

(F) Dose-Response relationship for L-glutamate for GluR3$_{flip}$ (in the presence of 100 μM cyclothiazide, white circles), R6TM1R3$_{flip}$ (black squares) and R3(R6S1)$_{flip}$ (black triangles) recorded in a whole-cell mode. Currents were normalized to the response at 10 mM. EC_{50} and hill slope values (n) were estimated by fitting the concentration/current relationship with the equation $Y=1/(1+(EC_{50}/[Glu]^n))$ and were 148 μM /1.95 for GluR3$_{flip}$, 155 μM/n=1.66 for R6TM1R3$_{flip}$ and 107μM/n=2.02 for R3(R6S1)$_{flip}$, respectively. Data are from 5-9 cells each (at -60 mV). Error bar

represents SE. Inset shows typical responses of a cell transfected with $R3(R6S1)_{flip}$ to a series of glutamate concentrations. The order of concentrations were: control, .03, .1, .03, control .2, .3 and 10 mM).

Figure 3: Desensitization properties of GluR3-'S1' chimeras.

(left column) Map of chimeras and point-mutations. (A) Respective S1 regions are shown in black (GluR3) and white (GluR6). The junction residues, given by their number, are shown above each bar and correspond to the color code. (B) GluR3-'C1' residues, 515-548, are shown in single letter code. Letters in 'C1' mutants indicate the GluR6 amino acid exchanges and their position. Middle column; typical current responses to a 1s-application of 10 mM glutamate. Vertical scale bars were omitted for display purposes. Peak response sizes ranged from 4-660 pA. Right column; peak/Steady-State-(P/S)-, desensitization rate (R_D)- and resensitization rate (R_R) values ± standard error from 5-22 measurements each. Stars under the values indicate significant differences compared to $GluR3_{flip}$ (*$p<0.05$; **$p<0.01$; ***$p<0.0001$)

Figure 4: Mutations of T504A, L507Y, and E511K on $GluR3_{flip}$ differentially control desensitization and agonist binding.

GluR6 residues that replace GluR3 residues are indicated by one letter code above each trace. (A) a response from a patch containing receptors with the triple point mutations T504A , L507Y, and E511K. Specific values obtained from 13 measurements were: P/S=1.51±.07, R_D=50.3±8 s^{-1}. (B) representative responses from receptors containing the L507Y mutation alone (middle: P/S=1.01±.01, n=12) and in combination with T504A (left: P/S=1.09±.04, n=8) or E511K (right: P/S=2.1±.14, R_D=8.6±.45 s^{-1}, n=21). (C) representative

responses from receptors mutated in T504A (left: P/S=26.0±5.1, R_D=90.3±7 s^{-1}, n=11), E511K (right: P/S=43.3±8, R_D=90.3±7 s^{-1}, n=11) or combined (middle: P/S=30.7±7.2, R_D=186±43 s^{-1}, n=9). All receptors were activated by 10 mM glutamate, except for those containing the T504A mutation where a concentration 90 mM has been used. (D) Superimposed responses from a patch containing R3(T504A) to 1 mM quisqualate, 10 mM and 90 mM glutamate as indicated. L-Quisqualate (1 mM) -induced desensitization was similar to desensitization evoked by glutamate (P/S=24.0±7.1, R_D=360±68 s^{-1}, n=8) (E) Dose-Response relationships to glutamate of the mutants shown in panels A-C (indicated by letter code on each trace) were measured as described in Figure 1F; desensitizing receptors were measured in presence of 100 µM cyclothiazide. EC_{50} and hill slope values (n) were: L507Y (-Y-)=48 µM/n=1.66; L507Y+E511K (-YK)=131 µM/n=1.52; E511K (--K)=236 µM/n=1.64; T504A+L507Y (AY-)=2.09 mM/n=1.64; T504A+L507Y+E511K (AYK)=9.6 mM/n=1.48; T504A (A--)=19.9 mM/n=1.81; T504A+E511K (A-K)=21.2 mM/n=1.81.

Figure 5: Specificity of L507 for AMPA receptor desensitization

(A-D) a typical response to application of 10 mM glutamate, at -60mV, obtained from a patch containing the mutant GluR1(L497Y)$_{flip}$ (A), GluR6(Y521L) (B), and R6TM1R3(Y521L) (C). (D) Glutamate evoked current in the presence of 100 µM cyclothiazide from the same patch as in panel C.

Figure 6: Aromatic residues in position 507 remove desensitization

(A-C) a typical response to application of 10 mM glutamate, at -60mV, obtained from a patch containing the GluR3$_{flip}$ mutant L507F (A), L507S (B) and L507T (C). Inset in C shows the same trace on a

faster time scale. The time constant of desensitization is 0.72 ms. (D) desensitization rate R_D for various substitution at 507, indicated by one letter code for the respective amino acid. Significant deviations from the native receptor R3(L507), left are indicated with an asterisks.

Figure 7: Kainate elicits fast desensitizing responses at AMPA receptors.

(A) Plot correlates the efficacy of kainate currents (expressed as the ratio of peak kainate current to peak glutamate current) to the Peak/Steady-state ratio of glutamate currents from all receptors examined in figures 1 and 2 (represented as black circles). Correlation coefficient was 0.91. (B) A typical response to application of 5 mM kainate, at -60mV, obtained from the 16 fold slower desensitizing chimera R6TM1R3(Y521L). Data are from the same patch as shown in figure 4C-D. Insert exemplifies kainate current desensitization.

Figure 8: Alignment of partial amino acid sequences of different AMPA receptors (subunits) from rat, human and mouse

The relevant region of GluR1-4 from rat, GluR1-4 from human and GluR1 and 2 from mouse within the extracellular receptor binding region S1 (Stern-Bach, 1994 cit. loci) are shown. The alignment has been carried out employing the Clustal program, method 250. The relevant leucine (see box) is enwrapped by two residues (e.g. T494 and R499 in the case of the rat GluR1) which are essential for glutamate binding in all AMPA-receptors (Uchino, FEBS Lett. 308 (1992), 253-257).

The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of scope of the invention.

Example 1: Vector construction and use of nondesensitizing AMPA-receptor GluR1L497Y and its expression in mammalian or Xenopus oocytes expression for identification and/or characterization of AMPA-receptor ligand activities

Production of Mammalian/ Xenopus Oocytes Expression vector pC3G: pC3G was made by replacing the polylinker region of pCDNA3 (InVitrogen; Catalog No V790-20) with the polylinker of pGEM-HE (Liman et al., 1992, Neuron 9:861-871).

Construction of R1(L497Y) in pC3G:

Mutagenic oligos:

```
                        Y    NruI
                        ---  ------
sense:     GCTCCCTTGACCATAACCtatGTtCGcGAGGAAGTCATCGACTTC
antisense: GAAGTCGATGACTTCCTCgCGaACataGGTTATGGTCAAGGGAGC
```

GluR1(flip) subcloned in the pGEM-HE vector (Promega) has been mutated using the method developed by Stratagene (QuickChange mutagenesis, catalog No. 200518) with the above oligonucleotides. The correct plasmid has been selected by the presence of the silent NruI restriction site, and verified by DNA sequencing. The mutated cDNA insert has been cut out from pGEM-HE, by EcoRI and NheI restriction enzymes, and subcloned in pC3G using the same restriction sites. The same vector can be used to either transiently transfect mammalian cell lines or to produce mRNA for injection into oocytes.

The glutamate receptor was transfected in cell lines HEK293 (Clements, Neuron 7 (1991), 605-613) using the calcium phosphate method as described in Chen and Okayama, Biotechniques 6 (1988), 632-638. The detection of transfected cells was facilitated by cotransfection of an EGFP marker gene (eg. pGreen latern™-1, Gibco#10642-015)). Transfected cells were visualized using a inverted microscope equipped with fluorescence and the detection of green fluorescent cells was performed using 480nm excitation and 520 nM emission filter set. Membrane currents from these cells were performed using standard patch clamp whole-cell or outside-out patch recording techniques (Hamill et al., Pflugers Archiv – European J. of Physiol. 391 (1981), 85-100. As shown in Figure 1A, typical responses from

membrane patches expressing the native wildtype AMPA-receptor GluR1 show a rapid desensitizing current by exposure 1s duration (black bar) of saturating concentrations of glutamate (10 mM). The peak current can only be observed when using a fast application system (Clements, 1991, loc. cit.), as under these conditions the drug application proceeds faster than the apparent receptor desensitization. In contrast, responses from rat GluR1 with the point mutation Leucine to Tyrosine at the position 497 shows a nondesensitizing response (Fig 1B). The gray bar scheme above the responses indicates schematically the position of the mutation in the primary receptor sequence (left N-terminus, right C-terminus, thick bars represent putative transmembrane regions, the first segment is extracellular (Hollmann and Heinemann, 1994). In whole cell recordings, agonist and antagonist activity measurements can be easily performed using the GluR1L497Y receptor as exemplified in Fig 1C. Glutamate is applied to the extracellular space at the concentration indicated above the black bars by exchanging the external solution to the appropiate agonist containing solutions. Since the receptor exhibit nondesensitizing responses, the solution exchange profile is neglegible for the activity measurement. Fig 1D shows the measured dose-response profile for the receptor GluR1L497Y using whole-cell measurements from 10 cells and two different specific AMPA-receptor agonists l-glutamate and L-Quisqualate.

Example 2: Construction of Chimeras and Mutants for further analysis

Chimeras N1-N6 and C1-C6 were made as previously described (Stern-Bach, loc. cit.). Chimeras were constructed by polymerase chain reactions according to the strategy of gene splicing by overlap extension (Horton, Gene 77 (1989), 61-68). Making use of the redundacy of the genetic code, primers for each chimer or mutant were designed so as to introduce diagnostic restriction enzyme cleavage sites, which allowed for rapid screening for mutant genotype. Chimeric and mutant cDNAs were confirmed by double-stranded sequencing with cDNA-specific oligonucleotide primers and were subsequently inserted in mammalian exprssion vector pcDNA 3G. Point mutations were synthesized using the PCR-based method described by the 'QuickChange' mutagenesis (Stratagene). All mutants were first

subcloned by an appropriate digest in GluR3$_{flip}$-pGEMHE (pGMHE from Promega), and subsequently moved into pCDNA3 (InVitrogen) for expression in mammalian cells. All mutations were verified by double-strand DNA sequencing. The original 'flop' module of chimeras R6TM1R3 and R3(R6S1) (Stern-Bach, loc. cit.) has been exchanged by the corresponding 'flip' module using a SalI/XbaI digest of GluR3$_{flip}$. R6TM1R3 is a chimera containing the backbone structure of rat AMPA-receptor GluR3 in which the N-terminal portion has been replaced by the N-terminal portion of the rat kainate receptor GluR6 (see schematic drawing fig. 2C. The receptor R3(R6S1) is the AMPA-receptor GluR3 with the first 154 amino acids preceeding the first transmembrane have been replaced by the related structure in the rat kainate-receptor GluR6 (see scheme Fig. 2D). Amino acid numbering starts from the first methionine of the open reading frame.

Example 3: Exchanging the Binding Domain S1 of GluR3 with S1 of GluR6 Results in a Fully Active, But Completely Non-Desensitizing Receptor.

AMPA- and kainate-type glutamate receptor-channels have characteristic desensitization and resensitization kinetics. These were measured in HEK293 cells transiently transfected with pcDNA3 vectors containing GluR3$_{flip}$ (an AMPA receptor) or GluR6 (a kainate receptor) cDNA. For all kinetic measurements outside-out patch recordings in combination with a rapid solution exchange system (Clements and Westbrook, Neuron 7 (1991), 605-613; Colquhoun, J. Physiol-London 458 (1992), 261-287) were employed in order to obtain solution exchanges faster than the rate of desensitization measured for these glutamate receptors. Patches were exposed to 0.5-2 s long pulses of saturating glutamate concentrations (10 mM).

In general, outside-out patches were obtained from the human embryonic cell line HEK293 (ATCC CRL 1573, USA) expressing homomeric channels composed of rat GluR3$_{flip}$, GluR6$_R$ or chimeras, 12-96 hours after transfection, using the $Ca_2(PO_4)_3$-method (Chen and Okayama, Biotechniques 6 (1988), 632-638). Transfected cells were detected as described (Margolskee, Biotechniques 15 (1993), 906-911). All kinetic measurements were obtained from outside-out

patches to maximize solution exchange rates. After excision of the patch, the patch was moved into a stream of a rapid perfusion system (Clements and Westbrook, loc. cit.; Colquhoun, loc. cit.). Solution exchange (20-80% to peak) was judged by open tip control by diluting the control solution with 2% water ranging from 0.3-0.6 ms. Experiments were performed at room temperature (20-25^{o} C). Repeated agonist application was done at 0.2-0.02Hz. Recovery from desensitization were measured by paired-pulse application of agonist. Pipettes were filled with a solution containing 150 mM CsF or CsCl, 20 mM HEPES, 10 mM NaCl, 10 mM EGTA, adjusted to 305 mOsm, pH 7.3. Holding potential was usually - 60 mV. Currents were amplified using an Axopatch amplifier 200 B (Axon Instr., USA), filtered at 1-10 kHz and digitized at 2-20 kHz using pClamp 6.0 (Axon Instr., USA) acquisition system. The extracellular medium contained 170 mM NaCl, 10 mM HEPES, 2-4 mM $CaCl_2$, 2-4 mM $MgCl_2$, adjusted to 330 mOsm, pH 7.25. Agonist solutions were made by mixing external medium with isotonic (330 mOsm, pH 7.3) agonist stock solutions by replacing NaCl with the agonist. Analysis was performed using Axograph 3.5 software, and exponential were fitted using the squared error method. Multiple measurements from one patch were averaged and the results were treated as one experiment. Significance of results were determined by analysis of variance followed by Dunns posthoc comparison and are indicated when $p<0.05$.

As shown in Figure 2A-B, applying the agonist at a holding potential of -60 mV, evoked a rapidly evolving and strongly desensitizing inward current for both GluR3 and GluR6 homomeric channels. The amount of desensitization expressed as the ratio of peak to steady-state amplitude (P/S) was 46.2±3.9 for $GluR3_{flip}$ (n=13) and 236±53 for GluR6 (n=14). For the rate of desensitization (R_D; the inverse of the desensitization time constant) 240±15.4 and 225±20 s^{-1}, respectively, was measured. Desensitization was blocked by cyclothiazide (100μM) and Concanavalin A (1μg/μl) when added to the agonist solution of $GluR3_{flip}$ or GluR6 respectively; resulting in P/S values close to 1 (not shown). The rate of recovery from desensitization (R_R) was measured in paired-pulse protocols and was ~50

times faster for $GluR3_{flip}$ than for GluR6 (29.9±7.1 s^{-1} and 0.57±0.06 s^{-1}, n=10 respectively). The kinetic characteristics of $GluR3_{flip}$ and GluR6 are consistent with published values and comparable to native channels (Trussell, Proc. Natl. Acad. Sci. USA (1988), 4562-4566; Sommer, loc. cit.; Heckmann, Biophysical Journal 71 (1996), 1743-1750; Traynelis and Wahl, J. Physiol. 503 (1997), 513-531).

In order to identify specific protein domains modulating receptor desensitization, responses to glutamate from chimeric GluR3-GluR6 receptors were analyzed (Stern-Bach, (1994) loc. cit.). In contrast to both parent receptors, one N-terminal chimera, termed R6TM1R3 (Figure 2C), in which the entire extracellular N-terminal region of $GluR3_{flip}$ was substituted by the corresponding region of GluR6, showed complete removal of desensitization (Figure 2C; P/S=1.02±.01, n=30).

Several studies have indicated that AMPA receptor desensitization is modulated by the 'flip/flop' region located in S2 (Sommer, 1990 loc. cit.; Mosbacher, 1994 loc. cit.; Partin, 1994 loc. cit.; Partin, 1995 loc. cit.). Analysis of the 'flop' version of chimera R6TM1R3 also showed complete removal of desensitization (P/S=1.07±.04; n=9, not shown), suggesting that the removal of desensitization does not require specific splice variants in the 'flip/flop' cassette.

Based on the homology to bacterial proteins and functional studies, the N-terminal region can be separated in two: the LIVBP-like domain and the agonist binding domain S1. These two regions were examined separately by measuring the kinetic properties of chimera R3(R6S1), in which the GluR6 exchange was limited to S1, and chimera R6KBPR3, in which the GluR6 exchange was limited to the LIVBP-like region. Chimera R3(R6S1) exhibited a fully non-desensitizing response (Figure 2d; P/S=1.01±.01, n=6), whereas chimera R6KBPR3 resulted in a receptor indistinguishable from GluR3 (P/S=56.2±22; R_D=232±44 s^{-1}; R_R=19.3±5.2 s^{-1}, n=6; not shown). The LIVBP-like region was recently reported to affect glycine-independent NMDA receptor desensitization (Krupp, 1998 loc. cit.; Villarroel, 1998 loc. cit.). To further test its possible role in desensitization, the kinetic properties of the reverse chimera R3KBPR6 and chimera NR1KBPR6, in which the LIVBP-like domain was taken from the NMDA receptor subunit NR1a (Stern-Bach, 1994 loc.

cit.), were also checked. These two chimeras desensitized in a manner similar to GluR6 (R3KBPR6: P/S=94.3±23, R_D=341±45 s^{-1}, R_R=0.24±0.07 s^{-1}, n=5; NR1KBPR6: P/S=83.1±33, R_D=411±73 s^{-1}, R_R=0.31±0.09 s^{-1}, n=4). Thus, abolishing desensitization in GluR3 by the chimeric exchange, is exclusively a result of replacing the agonist binding domain S1.

The possibility that the observed lack of desensitization for chimeras R6TM1R3 and R3(R6S1) could be due to some other form of kinetic change were excluded for three reasons. First, desensitization of AMPA receptors can be blocked by cyclothiazide. Since both chimeras carry the 'GluR3-flip' region important for cyclothiazide binding (Partin, 1995 loc. cit.; Partin, 1996 loc. cit.), any occluded desensitization should be revealed by an increase of the peak response in the presence of this drug. However, addition of 100 µM cyclothiazide to the agonist solution (a concentration which increases peak responses of $GluR3_{flip}$ up to three fold together with a complete block of desensitization; Partin, 1994 loc. cit.), resulted in an 14±4% and 12±3% inhibition of the peak response of R6TM1R3 (n=13) and R3(R6S1) (n=10) respectively. This inhibition is similar to that observed for AMPA receptors saturated with cyclothiazide, after rapid removal of the drug from the external solution (Partin, 1993 loc. cit.; Partin, 1994 loc. cit.). Second, the steady-state amplitude of a desensitized AMPA receptor is in the range of 2.5% of the peak response. Assuming similar channel densities, the responses from the chimeric receptor should be quite small. However, patch responses were 156±78 pA (n=30), ~13 fold larger than the average peak responses to GluR3, and ~3 fold larger than responses of GluR3 when treated with cyclothiazide. Third, a desensitized receptor state should be reflective in its single channel behavior by either smaller conductance states, shorter mean open times or longer shut times. On occasionally occurring patches that contained only a single chimeric channel, the channel opened to an apparent 23 pS state with a very high open probability (88.3±5%, at 10 mM glutamate); similar to the conductance behavior observed with GluR3 single channels treated with cyclothiazide.

Finally, since S1 is exclusively located on the extracellular site and is part of the ligand binding domain, mutagenesis may influence agonist binding but not ion

permeation. Consistent with that, no obvious differences in the current voltage properties between GluR3$_{flip}$ and the chimeras R6TM1R3 and R3(R6S1) were found (Figure 2E). Both chimeras responded to glutamate in a dose dependent manner which was similar to that observed for GluR3$_{flip}$ (Figure 2F and see also Stern-Bach, 1994 loc. cit.). As agonist potency strongly depends on receptor desensitization (Trussell and Fischbach, Neuron 3 (1989), 209-218; Patneau and Mayer, J. Neurosci. 10 (1990), 2385-2399; Patneau, J. Neurosci. 13 (1993), 3496-3509; Yamada and Tang, J. Neurosci. 13 (1993), 3904-3915; Partin, 1994, loc. cit.), desensitization of the native receptor GluR3$_{flip}$ was removed by coapplying the desensitization blocker cyclothiazide. Based on the lack of receptor desensitization, these measurements were carried out in whole-cell recordings that allowed a more accurate measurements of current amplitudes. Measurements were taken as described in Rosenmund, J. Neurosc. 15 (1995), 2788-2795. Potency values obtained from patches showed identical values and were thus pooled. Interestingly, cyclothiazide reduced glutamate potency from 155 μM to 398 μM for R6TM1R3 (n=5) and from 107 μM to 199 μM for R3(R6S1) (n=6). A similar reduction in affinity was observed for [^{3}H]AMPA binding to rat brain membranes when treated with cyclothiazide (Kessler, Mol. Pharmacol. 49 (1996), 123-131).
Taken together, these results show that abolishing desensitization in R6TM1R3 and R3(R6S1) does not result in gross alteration of other receptor-channel functions. It also suggests that desensitization is an active gating process independent from the process of activation.

Example 4: Three Distinct Regions in S1 Modify Desensitization Properties of GluR3 Receptors.

The S1 region of GluR6 consists of 162 amino acids, of which 79 are different from GluR3. In order to identify the residue(s) responsible for regulating desensitization, twelve new 'S1' chimeras, consisting of progressively smaller and complementary GluR6 substitutions (N1-N6 and C1-C6, Figure 3) were constructed. All of the functional C-terminal chimeras altered the desensitization properties of the GluR3 'parent'. Chimeras C6, C5, C3 and C2 did not desensitize, while C1 was partially

desensitizing (Fig. 3). The kinetics of 'C1' was significantly different from both $GluR3_{flip}$ ($p<.001$) and 'C2' ($p<.001$), suggesting that at least two sites within 'C2' modify desensitization.

The 34 amino acid region exchanged in 'C1' is proposed to include one of the hinge regions connecting the two agonist binding lobes (Stern-Bach, 1994, loc. cit.; Sutcliffe, Biophysical Journal 70 (1996), 1575-1589; Swanson, 1997, loc. cit.) and was recently found to be involved in glycine-independent NMDA receptor desensitization (pre-M1; Krupp, 1998, loc. cit.; Villarroel, 1998, loc. cit.). The role of the 12 residues in R3(R6S1C1) that are different from GluR3 were further examined, by grouping them into four different chimeras (C1a-d, Figure 3). In comparison to the 'C1' exchange, the desensitization of all 'C1a-d' chimeras were statistically different ($p<0.05$), suggesting that multiple combinations of mutations are required to produce the 'C1' phenotype.

In addition to the exchanges made at the C-terminus of S1, exchanges made at the N-terminus also modified desensitization properties of $GluR3_{flip}$. Chimeras 'N2', N3' and 'N4', but not 'N6' exhibited significant reductions in both desensitization and resensitization rates (Figure 3). Thus, residues located in the region between R417-Y474 may also be involved in desensitization.

Three distinct regions in S1 modify desensitization properties of GluR3 receptors. One is situated between R417-Y474 (cross of 'N4' and 'N6' exchanges), the second one between A501-D514 (cross of 'C2' and 'C1' exchanges) and the third one between F515-E548 ('C1').

Example 5: A Single Exchange in the Vicinity of Residues that Bind Glutamate Removes Desensitization of GluR3 Receptors.

The region substituted in the 'C2' chimera, excluding 'C1' (i.e. A501-D514) contains only three amino acids that differ between GluR3 and GluR6. These are T504A, L507Y and E511K (Figure 4). A simultaneous exchange of all these three amino acids resulted in a barely desensitizing receptor (Figure 4A). Exchange of single amino acid residues within these positions reveal that L507Y accounted entirely for the removal of desensitization (Figure 4B middle). Its effect was slightly

reduced when combined with E511K (Figure 4B, right) but not with T504A (Figure 4B; left). In addition to glutamate, quisqualate (1 mM; P/S=1.03±0.06, n=34) or AMPA (1 mM; P/S=1.05±0.03, n=24) also elucidated non-desensitizing responses with an identical efficacy of opening as glutamate (glutamate/quisqualate=1.02±0.02 and glutamate/AMPA=0.97±0.03, n=7, respectively). Desensitization was also abolished by the L507Y mutation when introduced into the flop version of GluR3 (P/S=1.01±.04, n=12; not shown). In contrast to the L507Y exchange, T504A, E511K or their combined exchange had no effect on the desensitization rate (Figure 4C) nor on the resensitization properties of $GluR3_{flip}$. Moreover, desensitization of these three later mutants, was completely blocked by cyclothiazide (100 µM). In contrast, cyclothiazide reduced peak response of L507Y by 9.6±2.7% and reduced the affinity for glutamate from 48 to 262 µM (n=6), similar as what was observed for the nondesensitizing chimeras R6TM1R3 and R3(R6S1).

Interestingly, it was found that all mutants containing the T504A exchange, evoked a weak response to 10 mM glutamate; usually a saturating concentration ($GluR3_{flip}$ receptors, Figure 2F). Responses evoked by quisqualate (1 mM) applied to the same patch usually about 3 fold larger compared to the response evoked by 10 mM glutamate (see Figure 4D). The difference between glutamate and quisqualate was observed on both desensitizing and nondesensitizing receptors. Since T504 is proposed to directly interact with glutamate (Stern-Bach, 1994, loc. cit.; Paas, Neuron 17 (1996), 979-990, Laube, Neuron 18 (1997), 493-503) and resides near R509, a residue shown by mutagenesis to be critical for agonist binding (Uchino, FEBS Lett. 308 (1992), 253-257) it was tested whether a change in glutamate efficacy or affinity had occurred. Dose-response analysis revealed that all mutants containing the T504A substitution exhibited more than 50 fold increase in the EC_{50} for glutamate (Figure 4E). The responses at saturating concentrations equaled the response amplitude of quisqualate (Figure 4D), indicating that the efficacy of channel opening was not affected by the mutation T504A.

The effects on glutamate potency of both positions T504A and L507Y were independent to each other, as the introduction of the T504A mutation led to a parallel reduction of potency (Y>AY=44-fold, YK>AYK=73-fold; K>AK=90-fold; Figure 4E), suggesting that the mechanism of the affinity shift were independent. In summary, the mutations in the region T504-E511 reveal an intriguing convergence of agonist binding and receptor desensitization.

Example 6: Specificity of Position L507 to AMPA Receptor Desensitization.

The AMPA receptor subunits GluR1-4 share high sequence homology in the S1 region (>85%), suggesting that a leucine to tyrosine exchange on other AMPA receptor subunits as well as in native AMPA receptors, would lead to the same phenotype. As shown in Fig. 5A, desensitization of the point mutant GluR1 L497Y is blocked with rapid application of 10 mM L-glutamate (see also Fig. 1C). This behavior is identical to the block of desensitization in the point mutant in AMPA-receptor GluR3 L507Y (Fig. 4B, middle trace). Thus, as shown hereinabove, block of desensitization is not limited to the AMPA-receptor subunit 1, but is also applicable to other AMPA-receptor subunits such as GluR3, GluR2 or GluR4. This is also not surprising, as the region in which the mutation is performed is to 100% identical between all AMPA-type Glutamate receptors (Fig. 9). The point mutation is very specific for AMPA receptors compared to other glutamate receptors, as shown in Fig. 5B, as the reverse substitution tyrosine to leucine at the kainate receptor subunit GluR6 (the corresponding position is 521) does not affects kainate receptor desensitization (see for comparison Fig. 2B). The uniqueness and specificity of the herein identified position is further demonstrated by the introduction of the reverse point mutation for the chimera R6TM1R3 (which is nonesensitizing; Fig. 2C). The receptor R6TM1R3 (Y521L) does show desensitization properties similar to AMPA receptors. This result implies that Y521 is not involved in kainate receptor desensitization, although it was possible that a change to something other than leucine might have an effect. However, mutations of Y521 to glycine (n=7), valine (n=4) and glutamate (n=4) resulted in desensitization properties indistinguishable from GluR6 wild-type (not shown). Therefore, this particular site (R3-507/R6-521) appears to be specific for AMPA-

but not kainate receptor desensitization. In summary, the point mutation is highly unique within the AMPA-receptor subunit, is specific for the AMPA-receptors in the glutamate receptor family, but is shared within all AMPA receptor subunits GluR1-GluR4, based on the highly identical protein structure within the ligand binding domain. These results are thus identical to the observations made with GluR 1 point mutant L497Y.

As pointed herein above, to further test the specificity of site L507, a reverse mutation on the kainate receptor GluR6 was performed. Mutant R6(Y521L) was almost identical in its kinetics when compared to the wild-type GluR6 receptor (Figure 5B).

The 'N1' exchange (Figure 3) - which includes the L507Y mutation - resulted in a partially desensitizing receptor, similar as found for the double mutation L507Y+E511K compared to L507Y alone (Figure 4B-right vs. middle). Thus, the control of desensitization by position 507 may either be modulated by other residues, or position 507 is necessary but not specific for the control of desensitization. To test this, the effect of a reversed Y to L mutation on the non-desensitizing R6TM1R3 chimera was first measured (see Figure 2C). The resulting R6TM1R3(Y521L) receptor, gained back almost complete desensitization, but with a 16-fold slower rate (R_D=15.4±1.1 s^{-1}; P/S=11.5±2.1, n=8; Figure 5C). Desensitization was blocked by cyclothiazide (Figure 5D) and resensitization was not different compared to $GluR3_{flip}$ (R_R=14.2±4.2 s^{-1}, n=3), suggesting that the kinetic characteristics of mutant R6TM1R3(Y521L) resemble those of GluR3.

Next, the role of position E511 was further examined. Recent molecular modeling of the glutamate binding domain predict that the region T506-V512 is α-helical. Both L507 and E511 are situated on the surface of lobe 1 with about the same orientation. The interaction observed between these two sites could be thus explained by either specific interactions between positions 511 and 507, or by the option that the entire α-helix nonspecifically controls desensitization. It was tested whether a tyrosine residue at position 511 will also result in a non-desensitizing receptor. However, mutant R3(E511Y) exhibit desensitization properties

characteristic of the wild-type receptor (P/S=43.9±13; R_D=383±50 s^{-1}; R_R=27.9±8.0 s^{-1}, n=4). Taken together it can be concluded that L507 is specifically required for AMPA-type receptor desensitization to occur, but with an additional modulatory effect of surrounding residues on this position.

Example 7: Removal of Desensitization Requires the Exchange of L507 to an Aromatic Residue.

Placing tyrosine, a aromatic residue onto position 497 into the AMPA receptor GluR1 results in a nondesensitizing phenotype (Fig. 1B,C). Based on the identical structure of the ligand binding domain between the AMPA receptor GluR1 and another AMPA receptor GluR3 (Fig. 9), its desensitization properties and the nature of removal of desensitization can be further analyzed by introducing residues other than tyrosine at the corresponding position 507 of the AMPA-receptor GluR3 as shown in Fig. 6. Therefore, in order to understand the nature of the removal of desensitization by the L507Y mutation, residues other than tyrosine were introduced in this position (Figure 6). Of the 11 mutations tested, desensitization was blocked by three changes, to phenylalanine (F; P/S=1.08±0.11, n=7; Figure 6A&D), tryptophane (W; P/S=1.01±0.03, n=5; Figure 6D), and histidine (H; P/S=2.03±0.4, n=6; Figure 6D), all aromatic amino acids. The partial desensitization observed for mutation L507H may be due to the slightly smaller size of the imidazole ring rather than its protonation state since a similar behavior at different pH values was observed. Exchanges to the aliphatic alcohol side-chains serine (S; Figure 6B) and threonine (T; Figure 6C), resulted in fully desensitizing receptors, with a significant faster desensitization rate, R_D, for the L507T. A similar increase was also observed by the mutation to asparagine (N; Figure 6D). Finally, exchanges to the basic/positively charged lysine (K), acidic/negatively charged glutamate (E), or to the relative small side-chain valine (V) and glycine (G) had no apparent effect on desensitization when compared to $GluR3_{flip}$ (Figure 6D).

Example 8: Kainate Elicits Fast Desensitizing Currents at AMPA receptors.

A structural tie between agonist binding and desensitization could be the basis for the observation that AMPA receptor desensitization depends on the agonist used. Kainate applied to AMPA receptors, induces rapid, much weaker desensitizing responses, with considerably lower agonist efficacy than AMPA or glutamate (Patneau and Mayer, Neuron 6 (1991), 785-798; Patneau, 1993, loc. cit.). If kainate binding and activation induces conformations other than with glutamate (particular the one associated with desensitization), the degree of glutamate induced desensitization expressed by a receptor should not influence its kainate response. Responses evoked by saturating kainate concentrations (5-10 mM) from the GluR3-S1 chimeras (see Figures 2 and 3) were all essentially non-desensitizing. The efficacy of kainate was maximal for non-desensitizing receptors and was positively correlated (r=0.91) to the degree of inhibition of glutamate induced desensitization (Figure 7A). The fully desensitizing receptors exhibited a peak glutamate/kainate response ratio (G/K) of 53.2±5.3 (n=55), while for all non-desensitizing mutants G/K was 6.21±0.7 (n=66). The lack of apparent receptor desensitization, in contrast to native AMPA receptors (Patneau, 1993, loc. cit.), may result from desensitization kinetics that are considerably faster than those of activation, thus being either not measurable or overlooked. To test this idea advantage was taken of the 16-fold slower desensitizing receptor R6TM1R3(Y521L). Desensitizing responses to kainate were now apparent (Figure 7B, P/S=2.71±0.2; R_D=155±28 s^{-1}; n=6). Similar results were obtained from chimeras N1-N3 (Figure 3, n=21), indicating the validity of this aforementioned hypothesis. Kainate responses evoked on AMPA receptors appear rapidly desensitizing. Kainate as well as glutamate evoke the same kinetic changes in the different chimeric and/or mutant receptors of this invention. Therefore, the conformational changes that the receptor undergoes upon agonist binding occur regardless which agonist is employed. Differences in respect to the agonist may be the speed of the desensitization process, however.

PCT/EP99/07604
Max-Planck-Gesellschaft zur Förderung ....
Our Ref.: D 2234 PCT

Claims

1. A nucleic acid molecule encoding a (poly)peptide which has an amino acid sequence of a glutamate receptor of the AMPA-type and/or of a subunit of said receptor and functions as a non-desensitizing AMPA-receptor or as a non-desensitizing subunit thereof, wherein the leucine corresponding to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ is replaced by an aromatic amino acid.

2. The nucleic acid molecule of claim 1 which is
   (a) a nucleic acid molecule comprising a nucleic acid molecule encoding the (poly)peptide having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO:8, SEQ ID NO: 9, or SEQ ID NO: 10, wherein the leucine residue corresponding to position 497 of SEQ ID NO: 1, 5 or 9, corresponding to position 504 of SEQ ID NO: 2, 6 or 10, corresponding to position 507 of SEQ ID NO: 3, to position 505 of SEQ ID NO: 4 or 8, or corresponding to position 513 of SEQ ID NO: 7 is replaced by an aromatic amino acid;
   (b) a nucleic acid molecule comprising a nucleic acid molecule having the DNA sequence of SEQ ID NO: 11, SEQ ID NO. 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 or SEQ ID NO: 20, wherein the codon represented by nnn corresponds to a codon coding for an aromatic amino acid;
   (c) a nucleic acid molecule hybridizing to the complementary strand of a nucleic acid molecule of (a) or (b); or

(d) a nucleic acid molecule being degenerate as a result of the genetic code to the nucleotide sequence of a nucleic acid molecule as defined in (c).

3. The nucleic acid molecule of claim 1 or 2 wherein the (poly)peptide comprises an aromatic amino acid at position 497 of SEQ ID NO: 1, 5 or 9, at position 504 of SEQ ID NO: 2, 6 or 10, at position 507 of SEQ ID NO: 3, at position 505 of SEQ ID NO: 4 or 8 or at position 513 of SEQ ID NO: 7, but differs therefrom by at least one mutation selected from the group consisting of amino acid substitutions, addition(s) insertions, deletions, inversions and/or duplications.

4. The nucleic acid molecule of any one of claims 1 to 3 derived from a rat, a mouse or a human.

5. The nucleic acid molecule of any one of claims 1 to 4, wherein said aromatic amino acid residue is tyrosine, phenylalanine, tryptophan or histidine.

6. The nucleic acid molecule of any one of claims 1 to 5 which is DNA, RNA or PNA.

7. The nucleic acid molecule of any one of claims 1 to 6 encoding a fusion protein.

8. A vector comprising the nucleic acid molecule of any one of claims 1 to 7.

9. A vector of claim 8 which is an expression vector, a gene targeting vector and/or a gene transfer vector.

10. A host transformed with a vector of claim 8 or 9 or comprising the nucleic acid molecule of claim 1 to 7.

11. The host of claim 10 which is a mammalian cell, an amphibian cell, an insect cell, a fungal cell, a plant cell or a bacterial cell.

12. The host of claim 11, wherein said mammalian cell is a HEK cell.

13. The host of claim 11, wherein said amphibian cell is an oocyte.

14. The host of claim 13, wherein said oocyte is a frog oocyte.

15. The host of claim 10 which is a non-human transgenic organism.

16. The host of claim 15, wherein said non-human organism is a mammal, amphibian, an insect, a fungus or a plant.

17. A method for producing the (poly)peptide encoded by a nucleic acid molecule of any one of claims 1 to 7 comprising culturing/raising the host of any one of claims 10 to 16 and isolating the produced (poly)peptide.

18. A (poly)peptide encoded by the nucleic acid molecule of any one of claims 1 to 7 or produced by the method of claim 17.

19. An antibody specifically directed to the (poly)peptide of claim 18, wherein said antibody specifically reacts with an epitope comprising the aromatic amino acid which replaces the leucine at position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of said wildtype rat AMPA receptor $GluR1_{flip}$.

20. The antibody of claim 19 which is a monoclonal antibody.

21. A composition comprising the nucleic acid molecule of any one of claims 1 to 7, the vector of claim 8 or 9, the (poly)peptide of claim 18 and/or the antibody of claim 19 or 20.

22. The composition of claim 21 which is a pharmaceutical composition, optionally further comprising a pharmaceutically acceptable carrier and/or diluent and/or excipient.

23. The composition of claim 21 which is a diagnostic composition, optionally further comprising suitable means for detection.

24. A method for the blocking of desensitization of a glutamate receptor of the AMPA-type, comprising the step of replacing a leucine corresponding to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ by an aromatic amino acid.

25. A method for identifying molecules which are capable of interacting with glutamate receptors of the AMPA-type, comprising the steps of
   (a) contacting a non-desensitizing AMPA-receptor as encoded by a nucleic acid molecule of any one of claims 1 to 7, a vector of claims 8 or 9, a host of any one of claims 10 to 16, or an antibody of claim 19 or 20 with said molecule; and
   (b) identifying among these molecules the molecules which are capable of interacting with said glutamate receptors of the AMPA-type.

26. A method for the characterization of molecules which are capable of interaction with glutamate receptors of the AMPA-type, comprising the steps of
   (a) contacting a non-desensitizing AMPA-receptor as defined in any one of claims 1 to 7, a vector of claims 8 or 9, a host of any one of claims 10 to 16, or an antibody of claim 19 or 20 with said molecules; and
   (b) measuring and/or detecting the characteristic effect said molecules evoke.

27. A method of screening for molecules which are capable of interacting with glutamate receptors of the AMPA-type, comprising the steps of

(a) contacting a non-desensitizing AMPA-receptor as encoded by a nucleic acid molecule of any one of claims 1 to 7, a vector of claim 8 or 9 or a host of any one of claims 10 to 16 with a candidate molecule; and

(b) measuring and/or detecting a response; and

(c) comparing said response to a standard response as measured in the absence of said candidate molecule.

28. A method for the production of a pharmaceutical composition comprising the steps of the method of any one of claims 25 to 27 and comprising a further step, wherein a derivative of said identified, characterized and/or screened molecule is generated.

29. A method for the production of a pharmaceutical composition comprising the steps of the method of any one of claims 25 to 28 and formulating the molecules identified, characterized, screened and/or derivatized in pharmaceutically acceptable form.

30. The method of any one of claims 25 to 29, wherein said molecule(s) comprise(s) (a) neuroprotective and/or (a) nootropic molecule(s).

31. The method of any one of claims 25 to 30, wherein said molecule(s) comprise(s) antagonist(s), partial antagonist(s), partial agonist(s) and/or agonist(s) for glutamate receptors.

32. Use of a non-desensitizing AMPA-receptor as encoded by the nucleic acid molecule of any one of claims 1 to 7 or use of a host as defined in any one of claims 10 to 16 as a biosensor for glutamate concentrations

33. Use of a non-desensitizing AMPA-receptor as encoded by the nucleic acid molecule of any one of claims 1 to 7 or use of a host as defined in any one of claims 10 to 16 for the characterization of glutamate receptor channel properties.

34. Use of a nucleic acid molecule of any one of claims 1 to 7, of a vector of claims 8 or 9, of a host of claims 10 or 11, of a (poly)peptide of claim 18, and/or of the antibody of claim 19 or 20 for the preparation of a pharmaceutical composition for preventing and/or treating neurological and/or neurodegenerative disorders.

35. The use of claim 33, wherein said neurological and/or neurodegenerative disorders are selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (FALS/SALS), ischemia, stroke, epilepsy, AIDS dementia and learning disorders.

36. Use of the nucleic acid molecule of any one of claims 1 to 7, the vector of claim 8 or 9, the host cell of claim 10 or 11 in gene therapy.

37. A kit comprising the nucleic acid molecule of any one of claims 1 to 7, the vector of claim 8 or 9, the host of any one of claims 11 to 16, the (poly)peptide of claim 18, the antibody of claim 19 or 20 or the molecule as identified, characterized or screened in any one of claims 25 to 31.

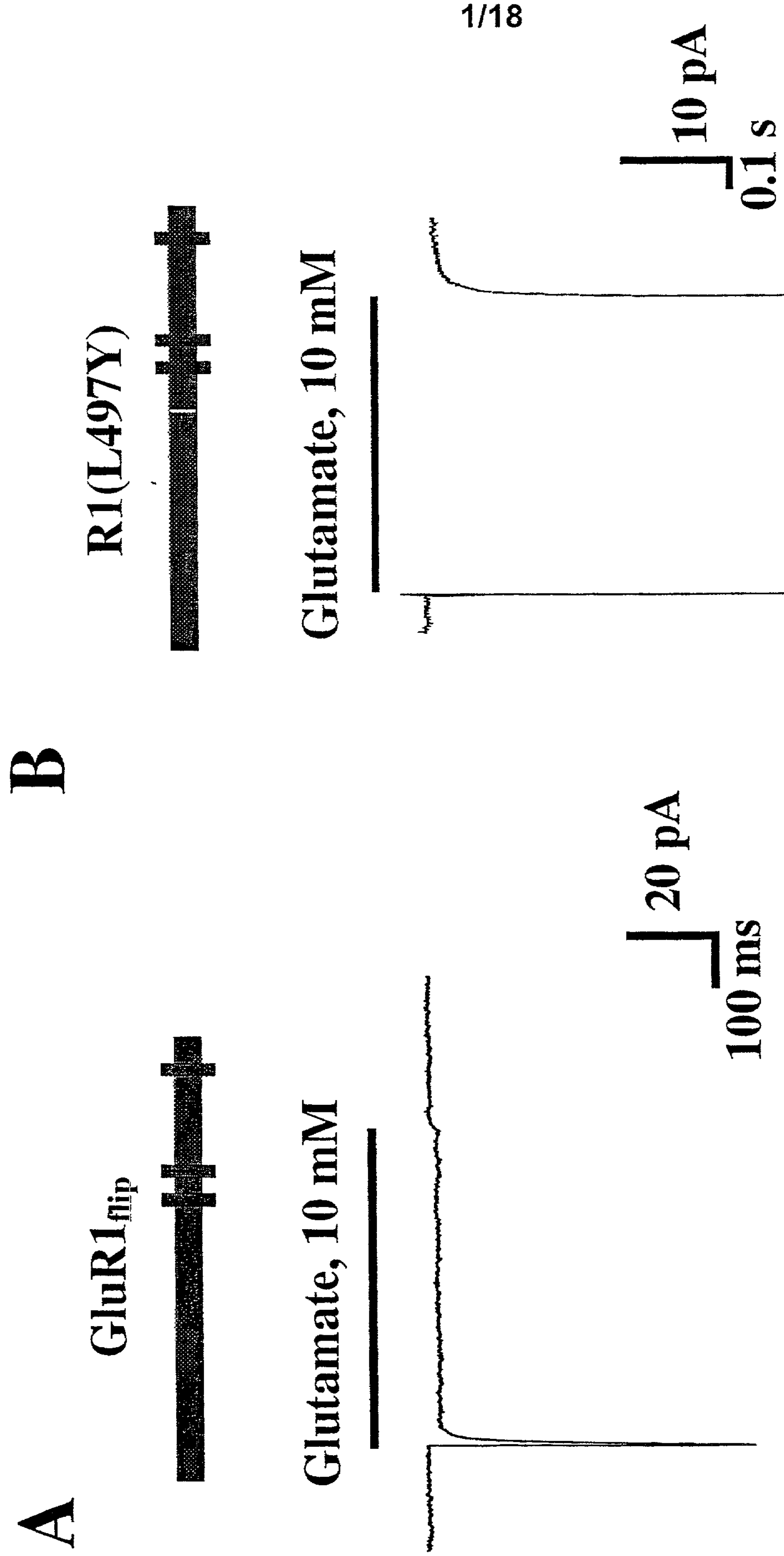

A
GluR1$_{flip}$
Glutamate, 10 mM
20 pA
100 ms
B
R1(L497Y)
Glutamate, 10 mM
10 pA
0.1 s

Figure 1

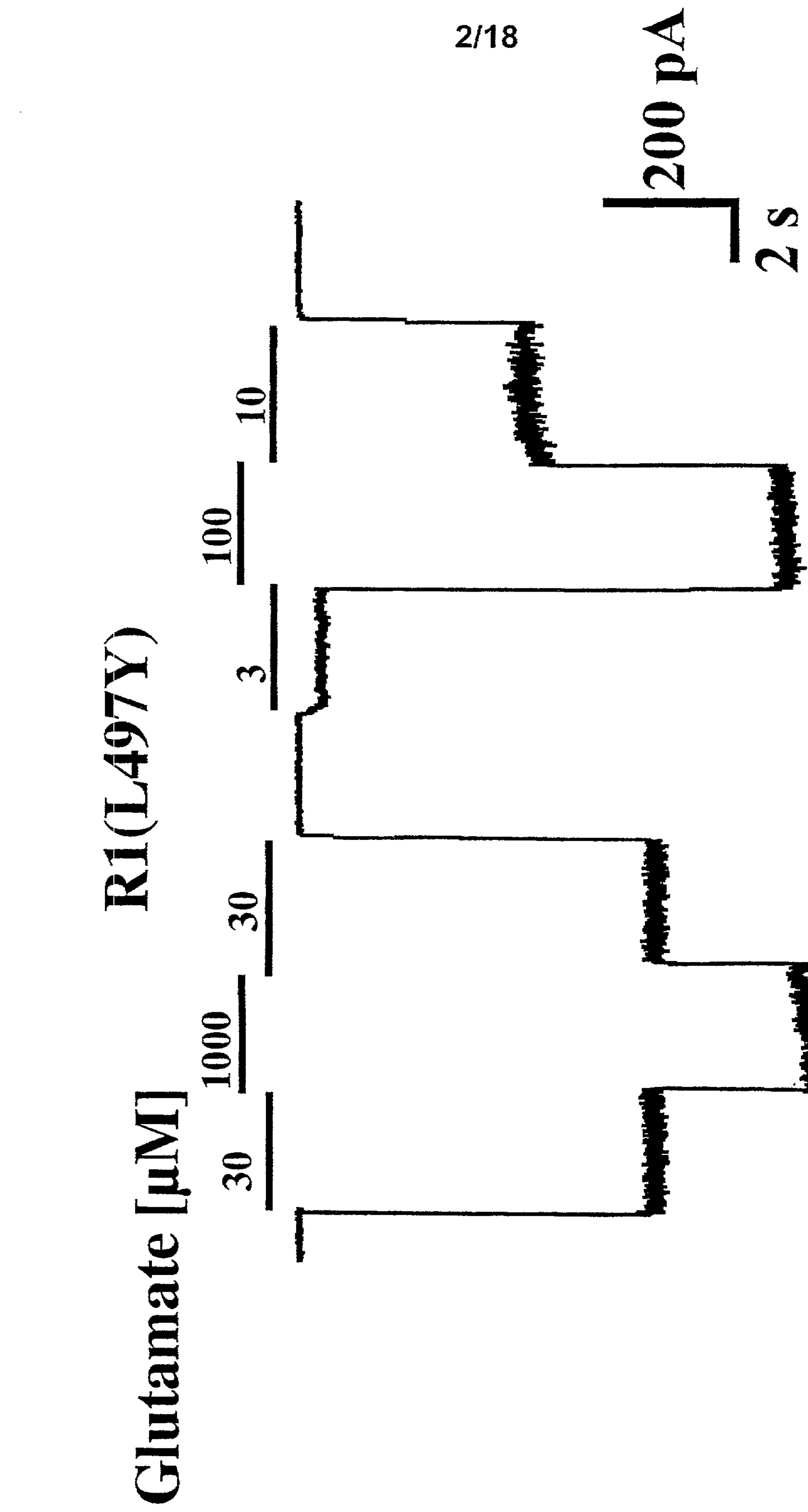


Figure 1 cont.

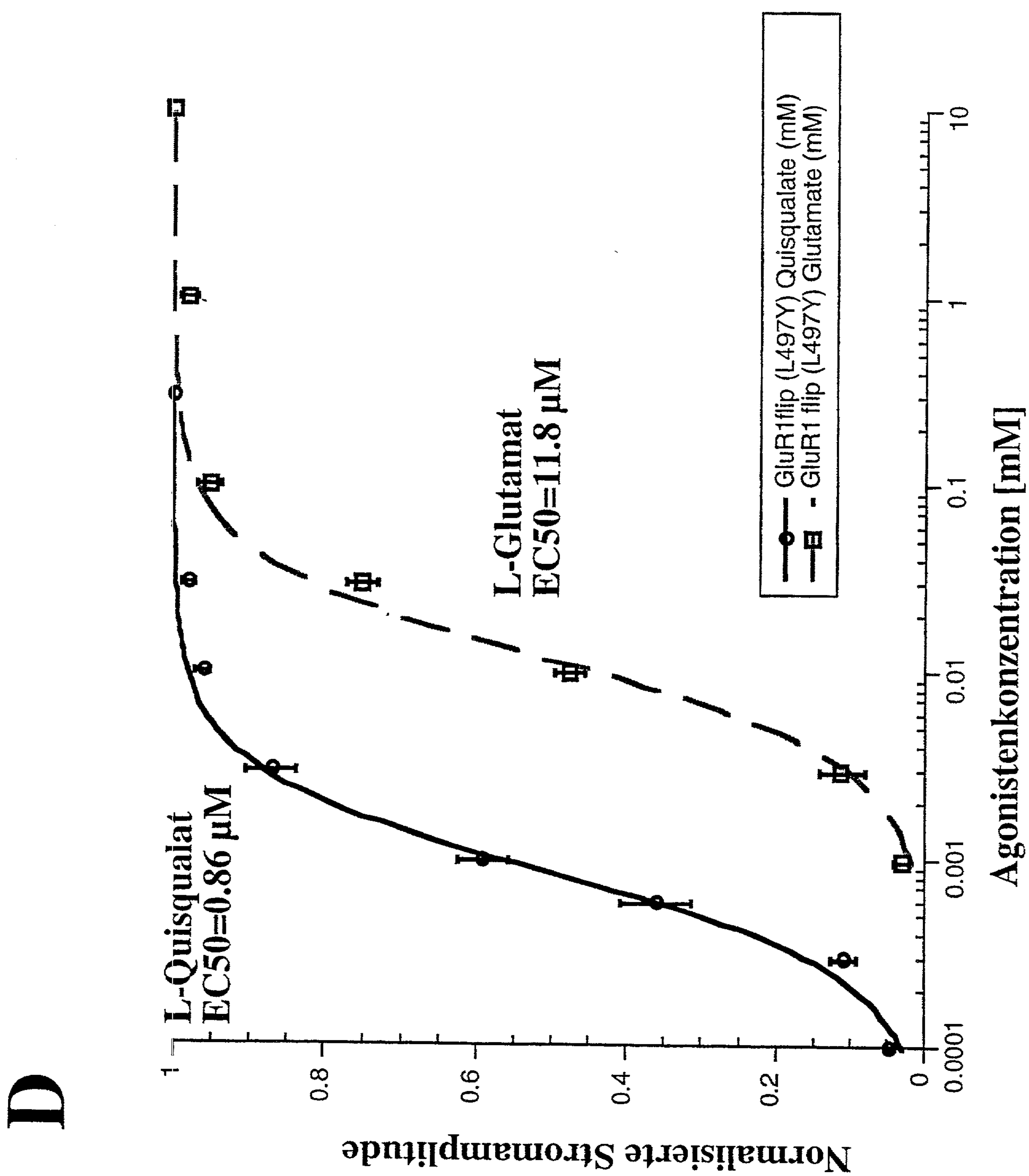


Figure 1 cont.

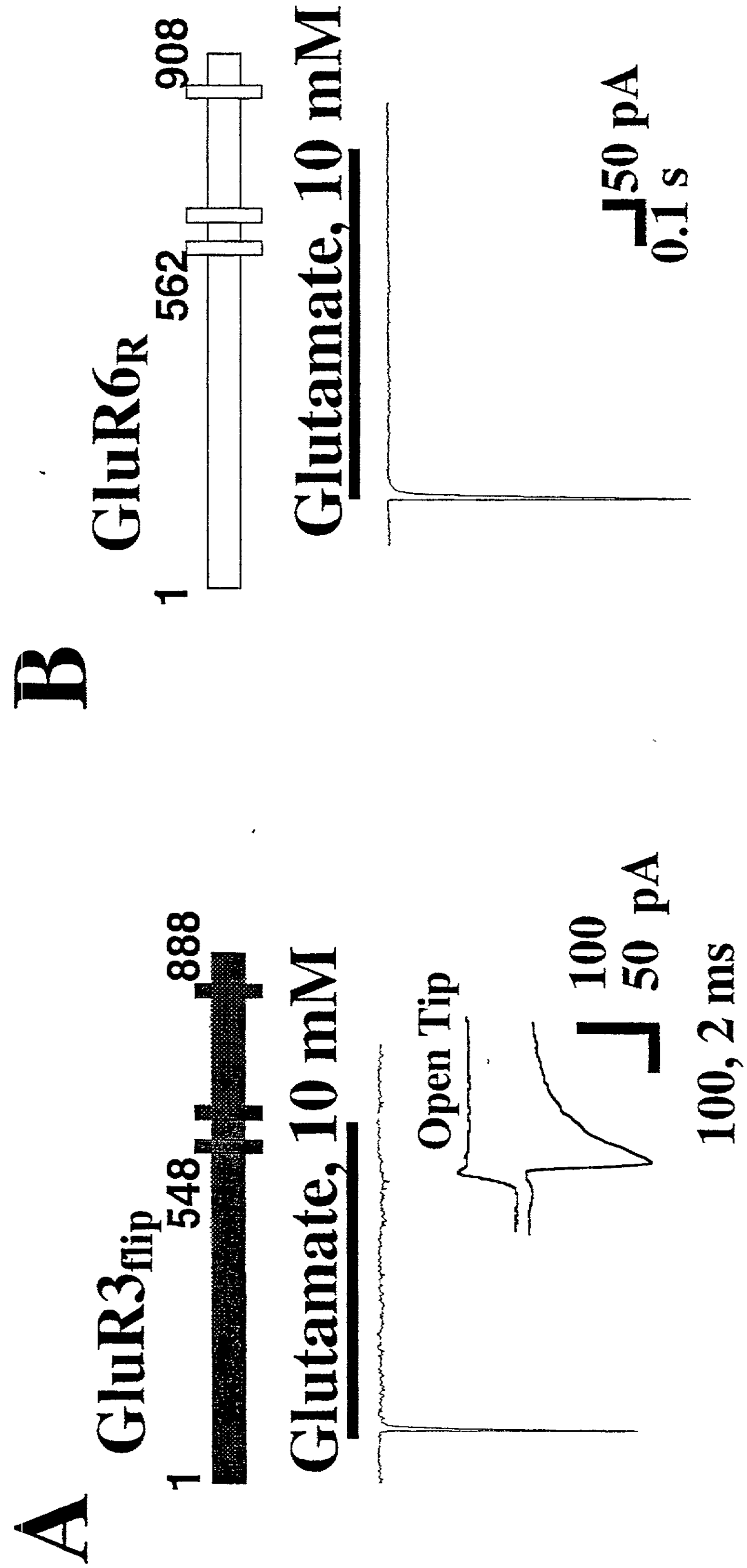

A
GluR3flip
1
548
888
Glutamate, 10 mM
Open Tip
100
50 pA
100, 2 ms
B
GluR6R
1
562
908
Glutamate, 10 mM
50 pA
0.1 s

Figure 2

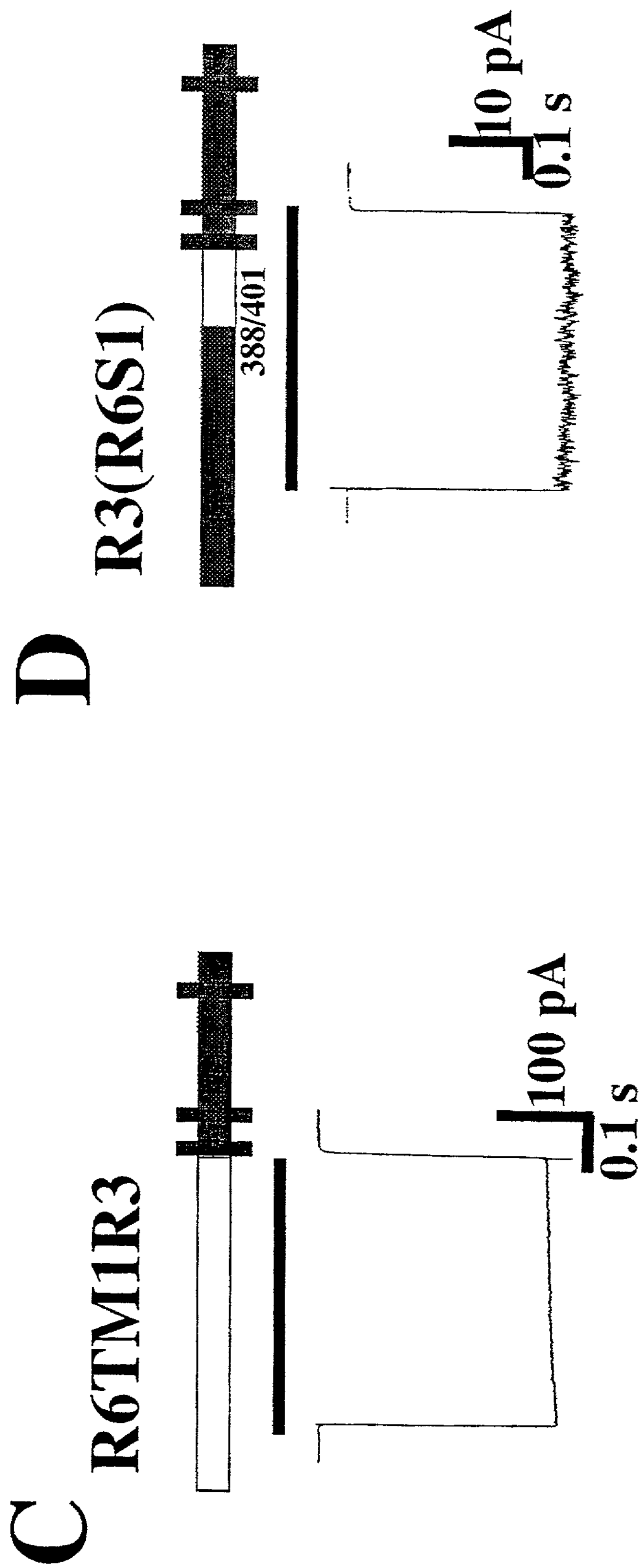


Figure 2 cont.

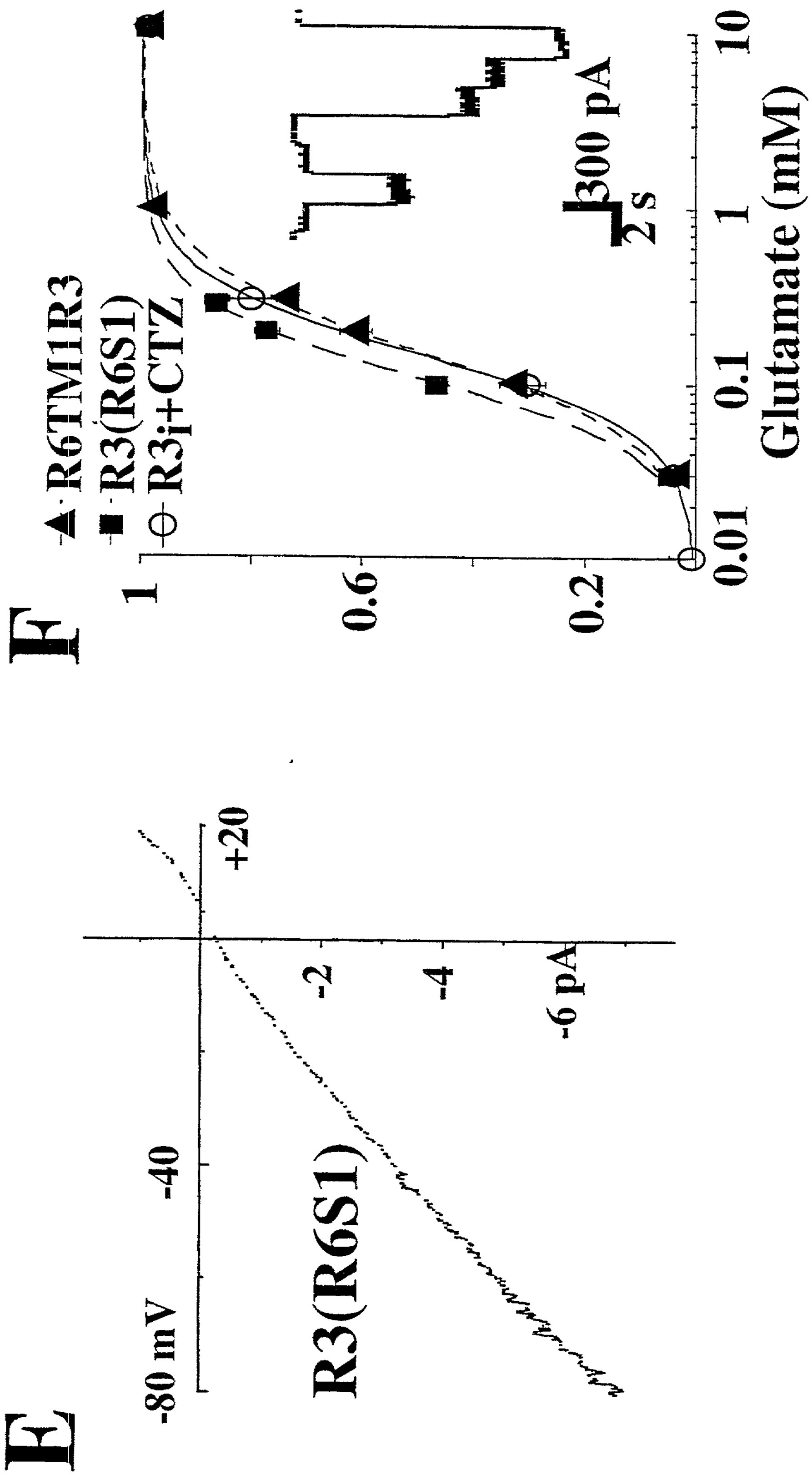
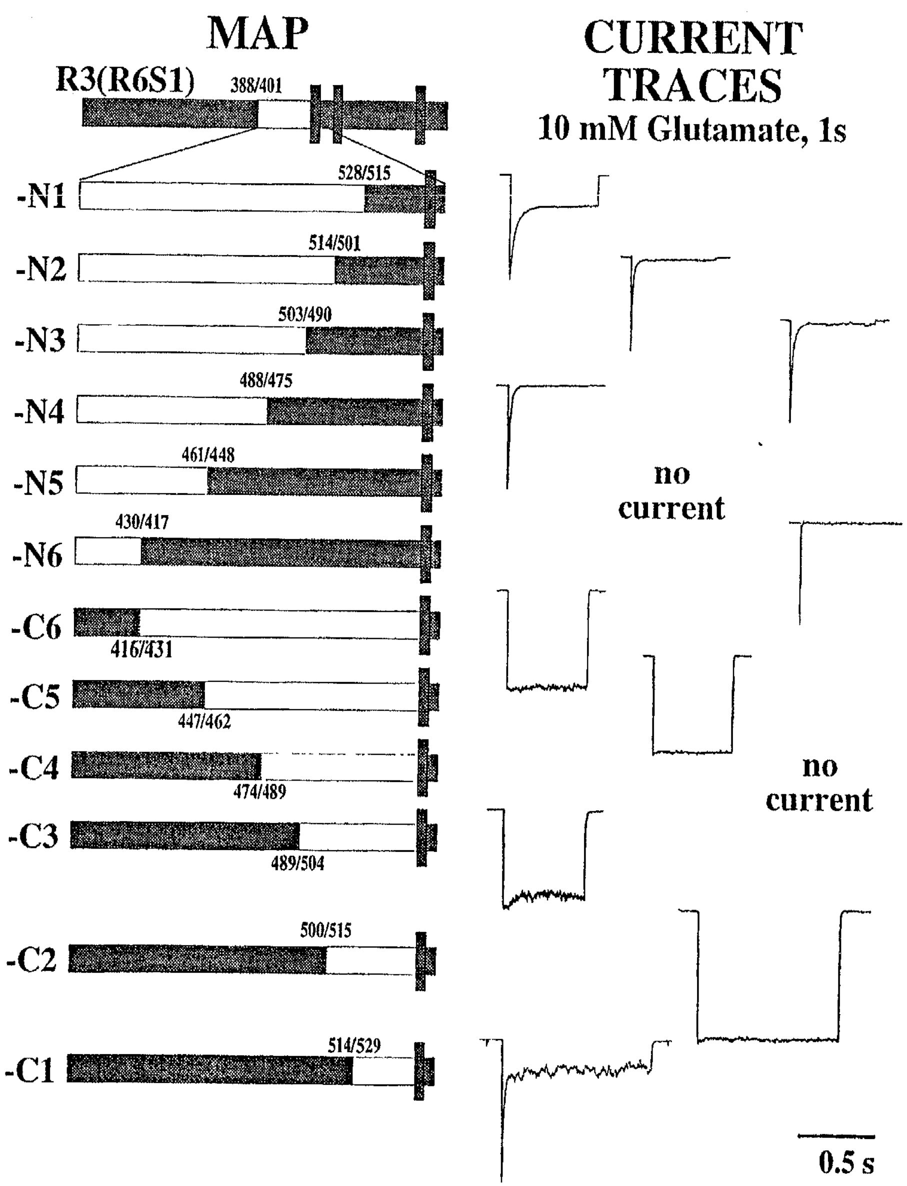


Figure 2 cont.



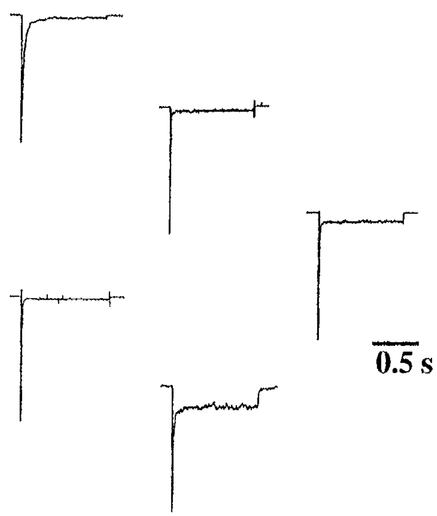
	PEAK/SS	R_D, s^{-1}	R_R, s^{-1}	n
-N1	3.35±0.2 **	15.6±0.6 *	26.6±3.7	9
-N2	25.8±3.5	28.4±4.9 *	2.8±0.5 ***	9
-N3	20.9±5.5	41.0±5.9 *	4.3±0.8 ***	16
-N4	46.0±9.0	29.2±1.2 *	7.2±0.9 **	20
-N5	--------	--------	--------	18
-N6	70.3±25	250±19	22±5.3	7
-C6	1.06±0.0 ***	2.07±0.6 ***	--------	5
-C5	1.20±0.0 ***	6.72±1.2 ***	--------	7
-C4	--------	--------	--------	16
-C3	1.32±0.2 ***	4.11±0.3 ***	--------	5
-C2	1.02±0.0 ***	2.04±0.6 ***	--------	18
-C1	3.07±0.2 ***	39.0±3.2 *	22.2±5.3	22

Figure 3

R3(R6S1C1) --T-----LYR--NGTN-------N--SPD

R3 515-FMSLGISIMIKKPQKSKPGVFSFLDPLAYE-548

CURRENT TRACES
10 mM Glutamate, 1s



	Sequence	PEAK/SS	R_D, s^{-1}	R_R, s^{-1}	n
C1a	--T----------------------------	57.6±16	190±12	32.6±3.2	11
C1b	---------LYR--------------------	155±49	383±50	42.0±6.8	14
C1c	--------------NGTN--------------	13.5±4.1*	99.2±6.1	19.2±6.3	15
C1d	-------------------------N--SPD	20.3±4.2	189±17	45.3±8.2	11
C1c/d	--------------NGTN-------N--SPD	90.4±33*	124±15	27.3±2.5	10

Figure 3 cont.

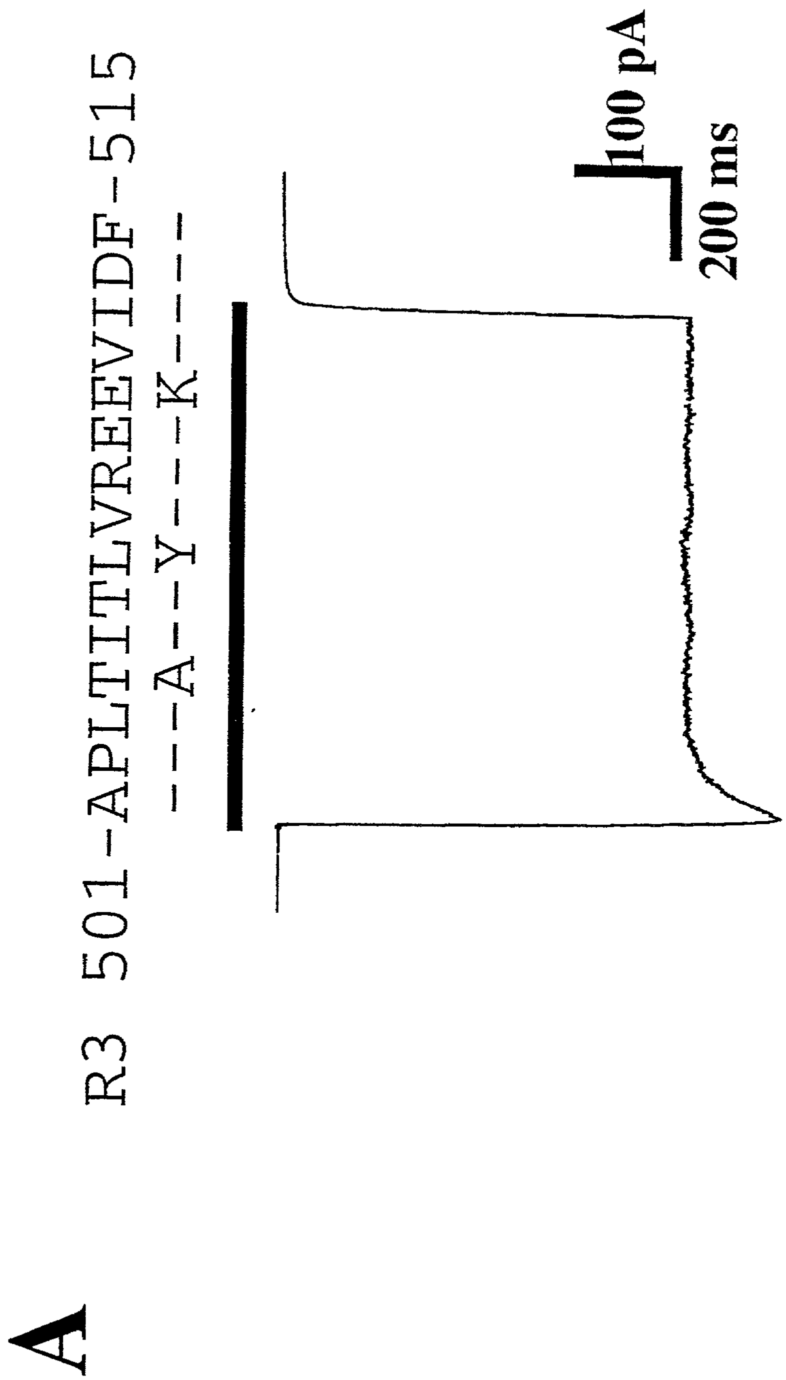


Figure 4

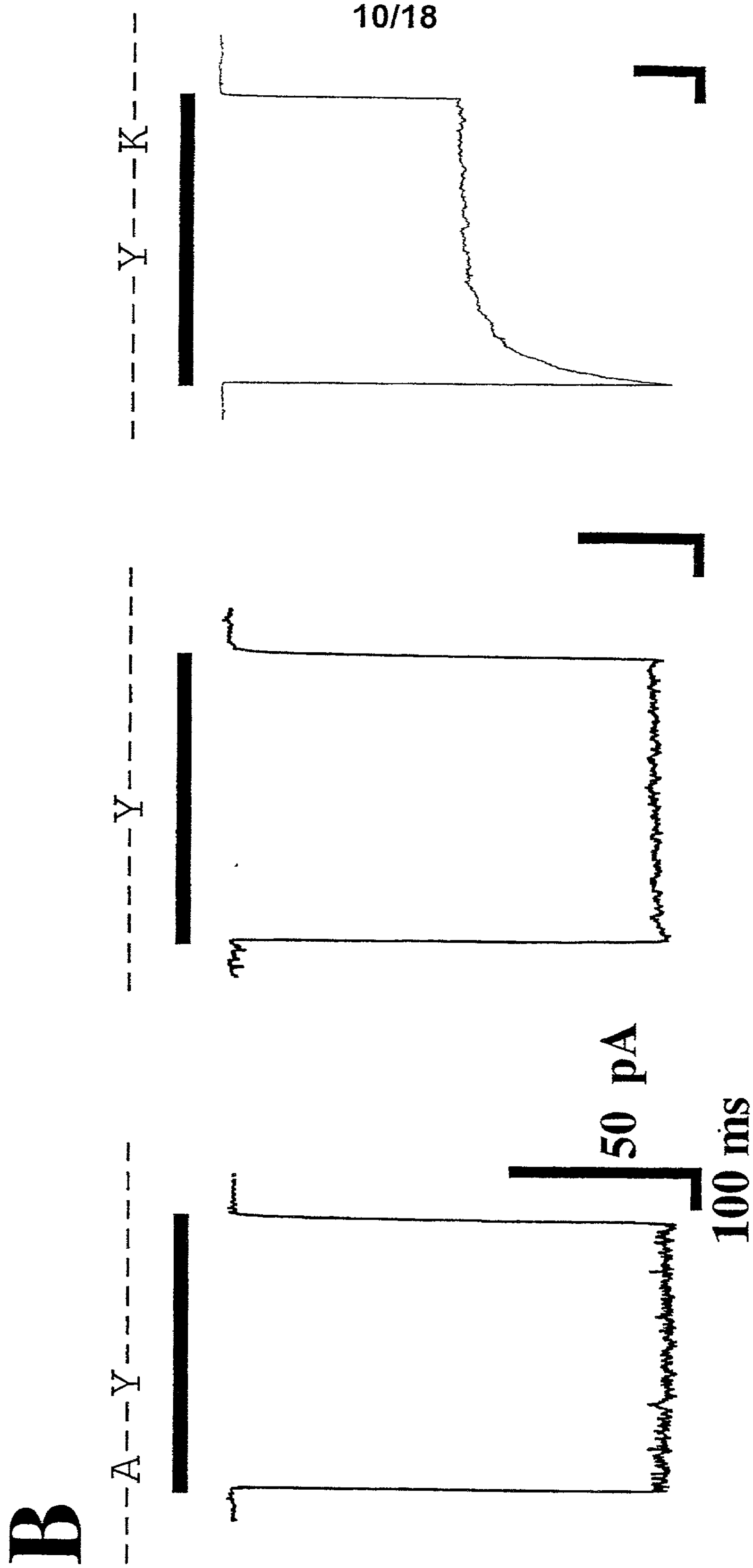


Figure 4 cont.

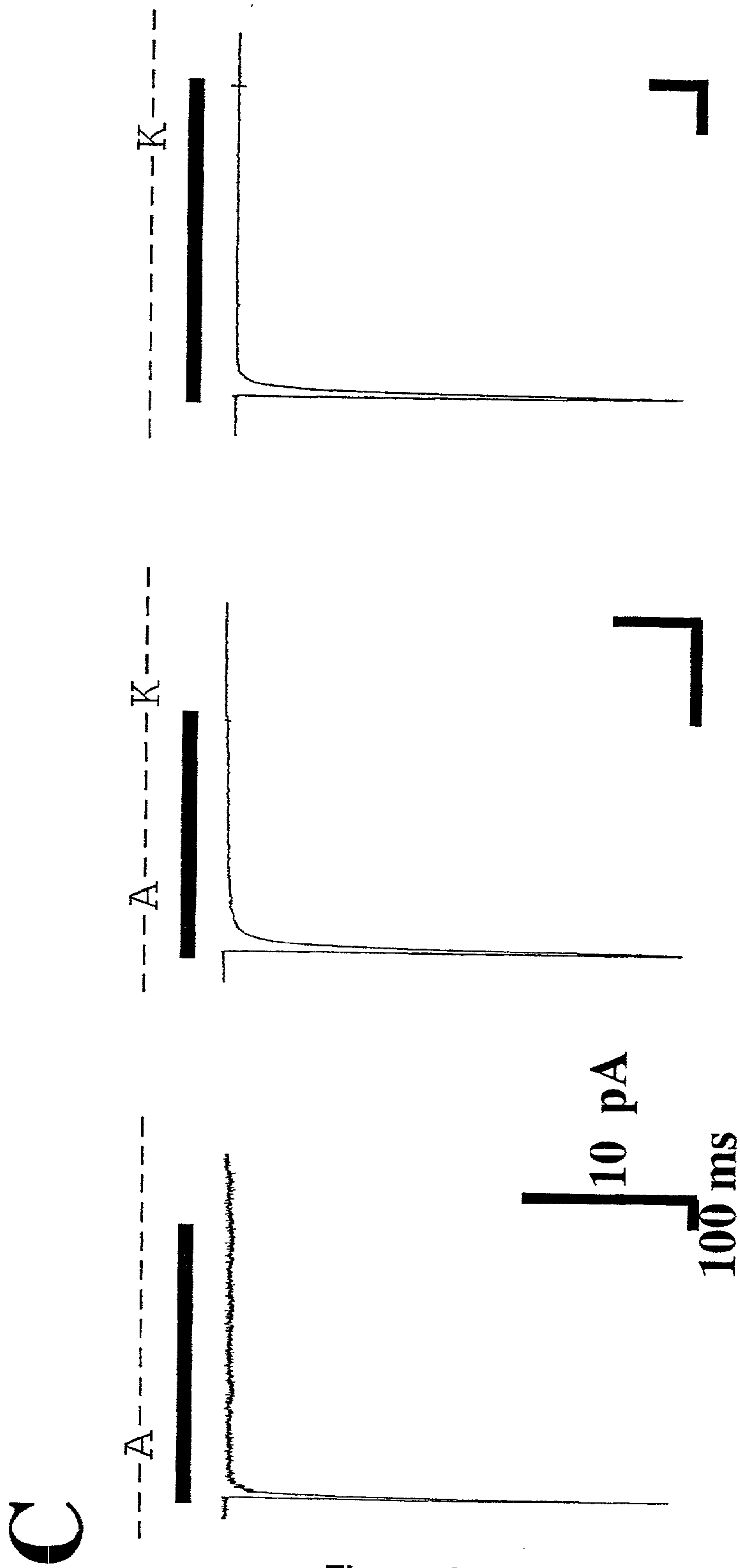


Figure 4 cont.

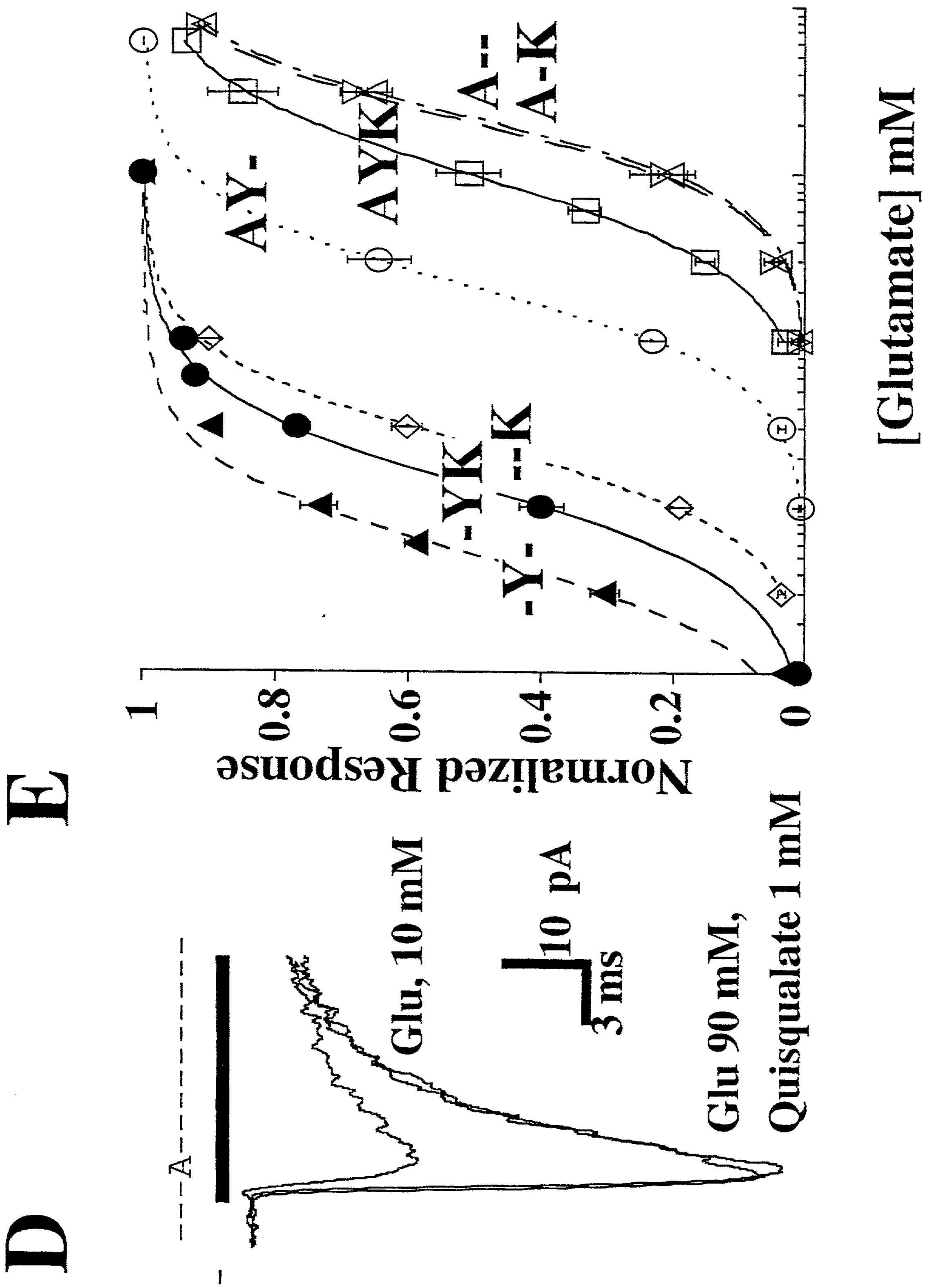


Figure 4 cont.

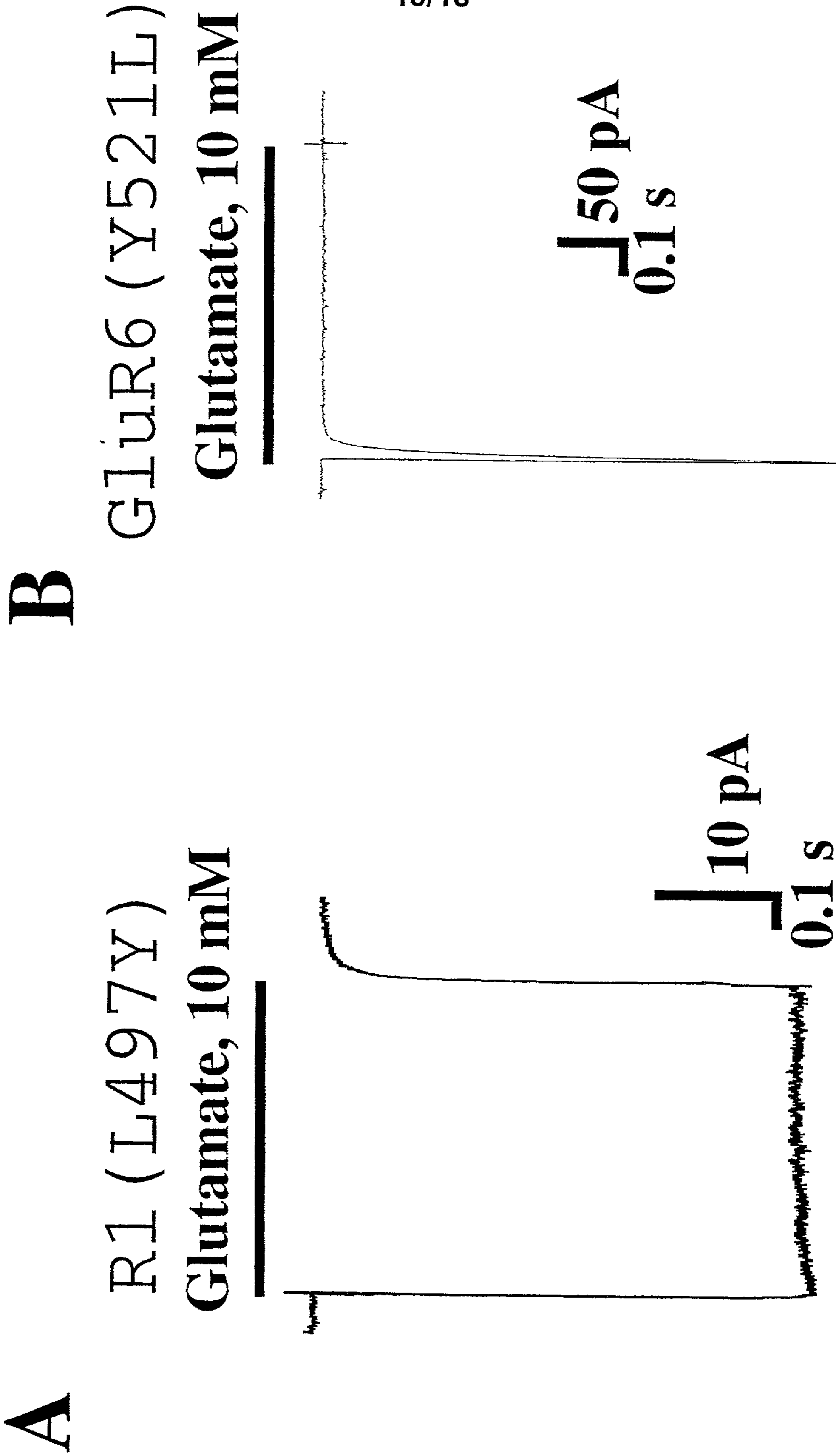

A
R1 (L497Y)
Glutamate, 10 mM
10 pA
0.1 s
B
GluR6 (Y521L)
Glutamate, 10 mM
50 pA
0.1 s

Figure 5

Figure 5 cont.

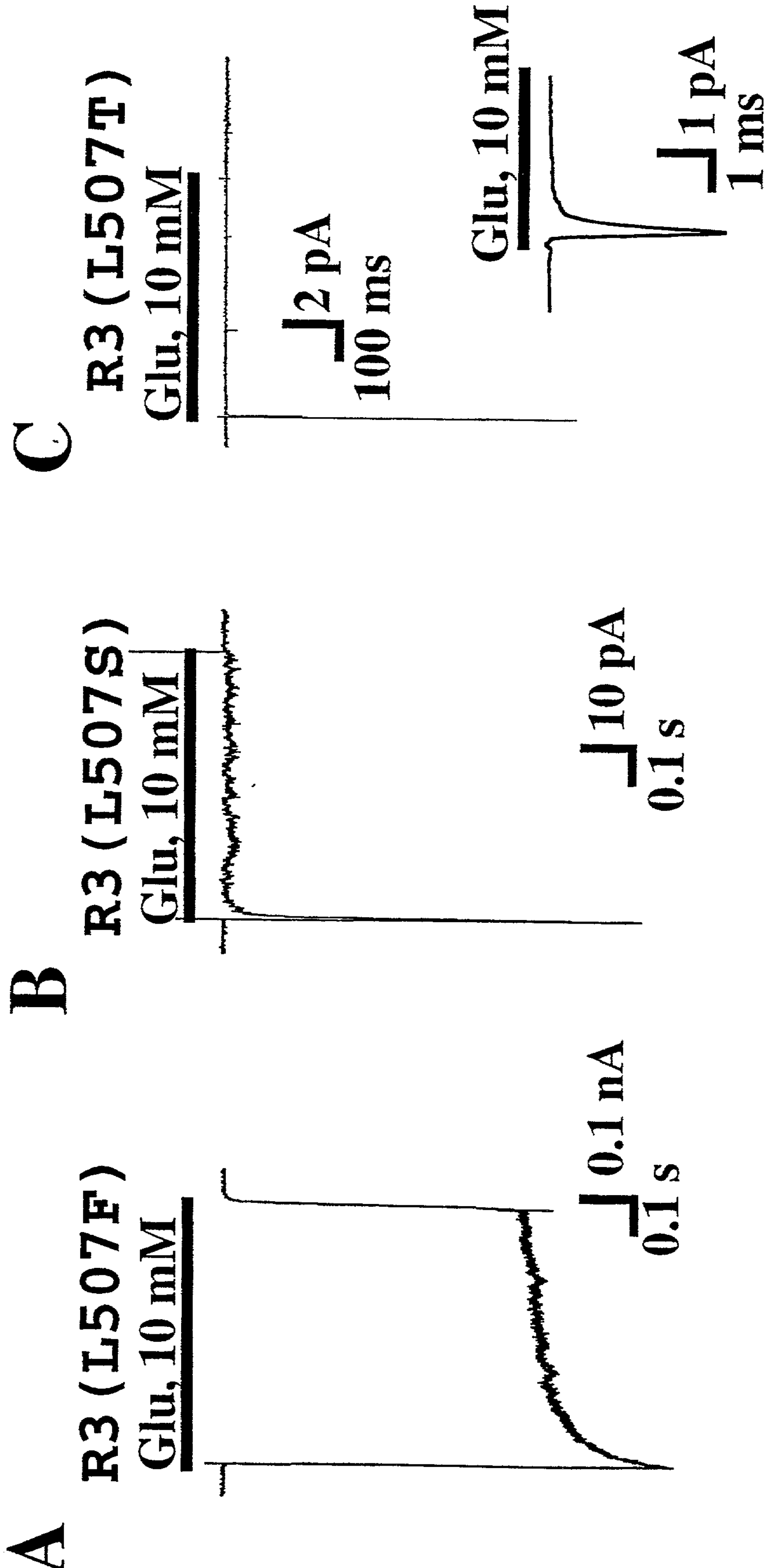

A
R3 (L507F)
Glu, 10 mM
0.1 nA
0.1 s
B
R3 (L507S)
Glu, 10 mM
10 pA
0.1 s
C
R3 (L507T)
Glu, 10 mM
2 pA
100 ms
Glu, 10 mM
1 pA
1 ms

Figure 6

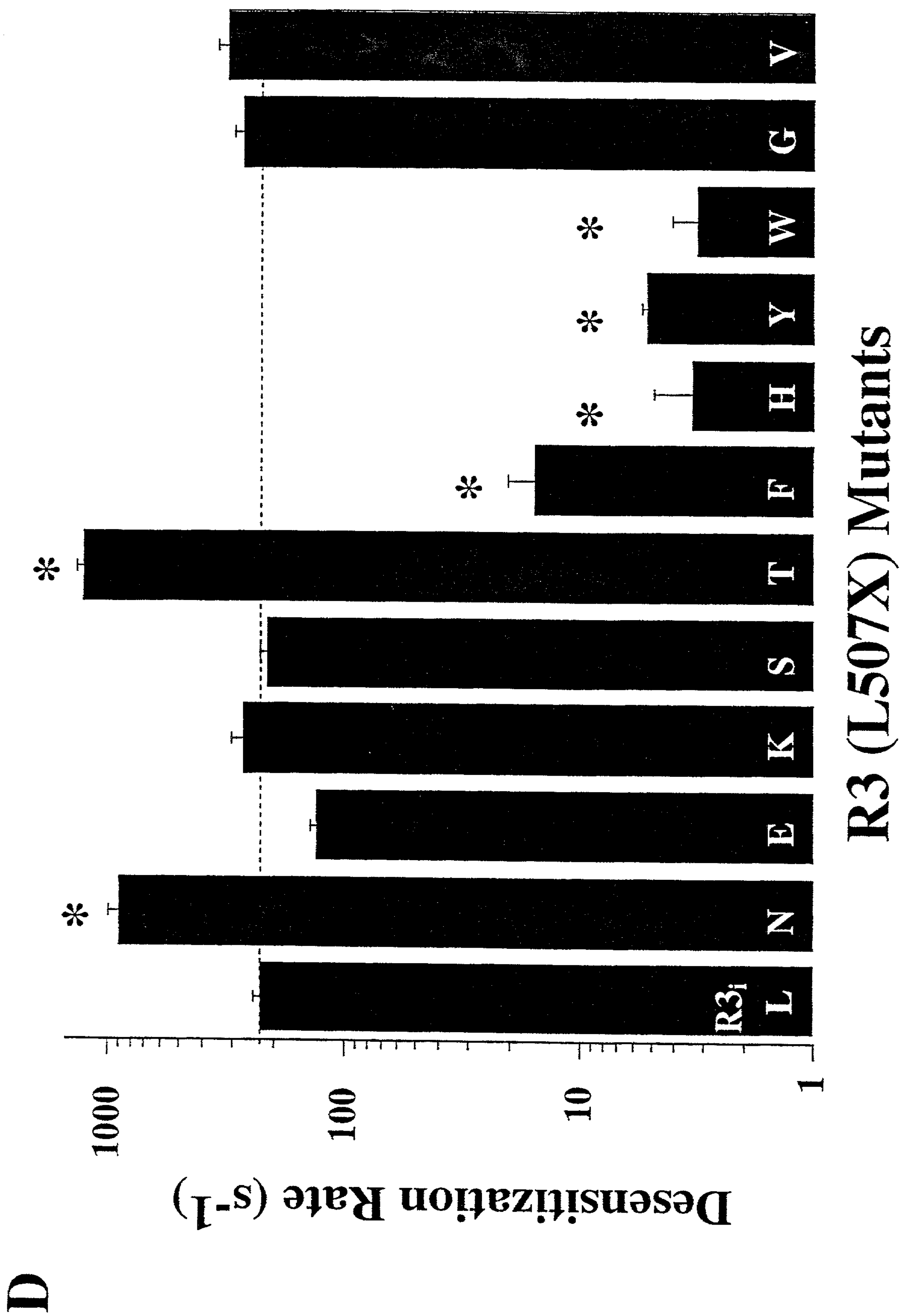


Figure 6 cont.

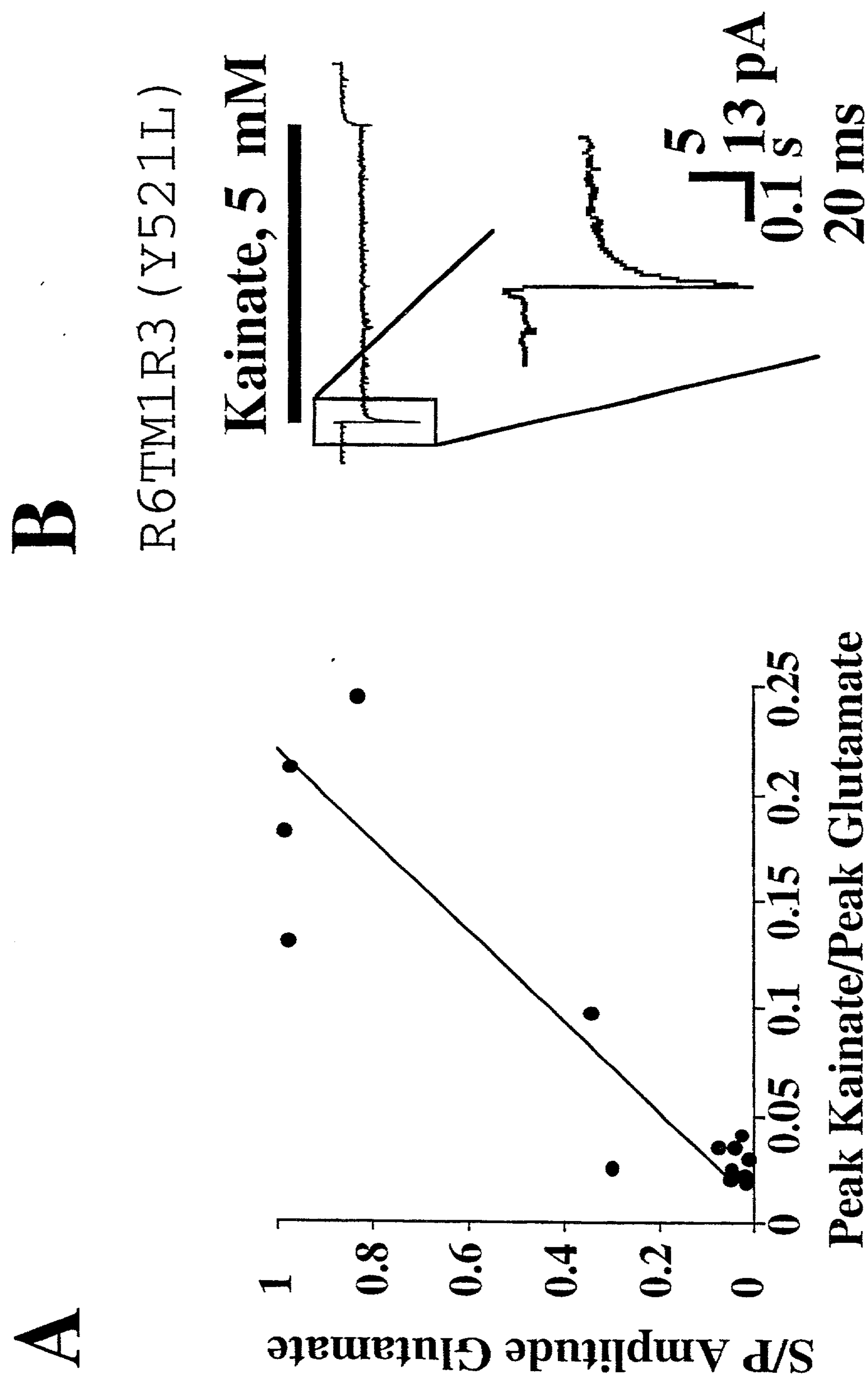

A
S/P Amplitude Glutamate
1
0.8
0.6
0.4
0.2
0
0
0.05
0.1
0.15
0.2
0.25
Peak Kainate/Peak Glutamate
B
R6TM1R3 (Y521L)
Kainate, 5 mM
5
13 pA
0.1 s
20 ms

Figure 7

09/807499

18/18

```
460 SDGKYGARDPDTKAWNGMVGELVYGRADVA rat GluR1
467 GDGKYGARDADTKIWNGMVGELVYGKADIA rat GluR2
470 GDGKYGARDPETKIWNGMVGELVYGRADIA rat GluR3
468 PDGKYGARDADTKIWNGMVGELVYGKAEIA rat GluR4
460 SDGKYGARDPDTKAWNGMVGELVYGRADVA hum GluR1
467 GDGKYGARDADTKIWNGMVGELVYGKADIA hum GluR2
476 GDGKYGARDPETKIWNGMVGELVYGRADIA hum GluR3
468 PDGKYGARDADTKIWNGMVGELVYGKAEIA hum GluR4
460 SDGKYGARDPDTKAWNGMVGELVYGRADVA m GluR1
467 GDGKYGARDADTKIWNGMVGELVYGKADIA m GluR2

490 VAPLTITLVREEVIDFSKPFMSLGISIMIK rat GluR1
497 IAPLTITLVREEVIDFSKPFMSLGISIMIK rat GluR2
500 VAPLTITLVREEVIDFSNAFMSLGISIMIK rat GluR3
498 IAPLTITLVREEVIDFSKPFMSLGISIMIK rat GluR4
490 VAPLTITLVREEVIDFSKPFMSLGISIMIK hum GluR1
497 IAPLTITLVREEVIDFSKPFMSLGISIMIK hum GluR2
506 VAPLTITLVREEVIDFSKPFMSLGISIMIK hum GluR3
498 IAPLTITLVREEVIDFSKPFMSLGISIMIK hum GluR4
490 VAPLTITLVREEVIDFSKPFMSLGISIMIK m GluR1
497 IAPLTITLVREEVIDFSKPFMSLGISIMIK m GluR2
```

Figure 8

VOSS1160

DECLARATION FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship is as stated below next to my name.

I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled NON-DESENSITIZING AMPA-RECEPTORS, the specification of which

____ is attached hereto.
_X_ was filed on April 13, 2001 (Attorney Docket No. VOSS1160)
as U.S. Application Serial No. 09/807,499
and was amended on ________
if applicable (the "Application").

I hereby authorize and request insertion of the application serial number of the Application when officially known.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

GTVS248750.1
105032-3

COUNTRY	APPLICATION NO.	FILING DATE	PRIORITY CLAIMED	
Europe	PCT/EP99/07504	October 11, 1999	✓ Yes	No
Germany	DE 198 47 064.1	October 13, 1998	✓ Yes	No

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

Full name of first inventor: Christian Rosenmund

Inventor's signature: [signature]

Date: September 10th, 2001

Residence: Mauerstrasse 18, 37073 Gottingen, GERMANY DEX

Citizenship: German

Post Office Address: Same as above

2-00

Full name of second inventor: Sebastian Russo

Inventor's signature: [signature]

Date: Sep. 10th 2001

Residence: Friedrichstrasse 1, 37073 Gottingen, GERMANY DEX

Citizenship: German

Post Office Address: Same as above

3-00

Full name of third inventor: Menahem Neuman

Inventor's signature: [signature]

Date: 18/10/01

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103052-3

PATENT
Attorney Docket No.: VOSS1160

In re Application of:
Rosenmund, et al.

Application No.: 09/807,499

IA Filing Date: October 11, 1999

Filed: April 13, 2001

For: NON-DESENSITIZING AMPA-RECEPTORS

POWER OF ATTORNEY BY ASSIGNEE

As a below-named assignee of the above-identified application ("Application"):

I hereby appoint the following attorneys of the assignee to prosecute the Application and to transact all business in the United States Patent and Trademark Office connected therewith:

JAMES CLEARY,	Reg. No. 45,843
TIM ELLIS	Reg. No. 41,734
CHARLES GAVRILOVICH, JR.,	Reg. No. 41,031
LISA A. HAILE	Reg. No. 38,347
KYLA HARRIEL,	Reg. No. 41,816
ERIC HOOVER,	Reg. No. 37,355
RICHARD J. IMBRA	Reg. No. 37,643
SHEILA R. KIRSCHENBAUM	Reg. No. 44,835
JUNE M. LEARN	Reg. No. 31,238
ALAN LIMBACH,	Reg. No. 39,749
GEORGE LIMBACH,	Reg. No. 19,305
KARL LIMBACH,	Reg. No. 18,689
TIMOTHY W. LOHSE	Reg. No. 35,255
TERRANCE A. MEADOR	Reg. No. 30,298
GERALD SEKIMURA,	Reg. No. 30,103
STEVEN R. SPRINKLE	Reg. No. 40,825
DAVID R. STEVENS	Reg. No. 38,626
MARK TAKAHASHI,	Reg. No. 38,631
EDWARD WELLER,	Reg. No. 37,468
RONALD YIN,	Reg. No. 27,607
BARRY N. YOUNG	Reg. No. 27,744

GT\6252046.1
105032-3

In re Application of:
Rosenmund, et al.
Application No.: 09/807,499
Filed: April 13, 2001
IA Filing Date: October 11, 1999
Page 2

PATENT
Attorney Docket No.: VOSS1160

I hereby authorize and request insertion of the application number of the Application when officially known.

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LISA A. HAILE, PH.D.
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LISA A. HAILE, PH.D.
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1600
San Diego, CA 92121

Yissum Research Development
Company of the Hebrew University

By: Nurit Inbar

Name: SECRETARY OF THE COMPANY

Title: NURIT INBAR

Date: SEPTEMBER 9, 2001

YISSUM
RESEARCH DEVELOPMENT COMPANY
OF THE
HEBREW UNIVERSITY OF JERUSALEM

PATENT
Attorney Docket No.: VOSS1160

In re Application of: Rosenmund, et al.	)
Application No.: 09/807,499	)
IA Filing Date: October 11, 1999	)
Filed: April 13, 2001	)
For: NON-DESENSITIZING AMPA-RECEPTORS	)

POWER OF ATTORNEY BY ASSIGNEE

As a below-named assignee of the above-identified application ("Application"):

I hereby appoint the following attorneys of the assignee to prosecute the Application and to transact all business in the United States Patent and Trademark Office connected therewith:

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KYLA HARRIEL,	Reg. No. 41,816
ERIC HOOVER,	Reg. No. 37,355
RICHARD J. IMBRA	Reg. No. 37,643
SHEILA R. KIRSCHENBAUM	Reg. No. 44,835
JUNE M. LEARN	Reg. No. 31,238
ALAN LIMBACH,	Reg. No. 39,749
GEORGE LIMBACH,	Reg. No. 19,305
KARL LIMBACH,	Reg. No. 18,689
TIMOTHY W. LOHSE	Reg. No. 35,255
TERRANCE A. MEADOR	Reg. No. 30,298
GERALD SEKIMURA,	Reg. No. 30,103
STEVEN R. SPRINKLE	Reg. No. 40,825
DAVID R. STEVENS	Reg. No. 38,626
MARK TAKAHASHI,	Reg. No. 38,631
EDWARD WELLER,	Reg. No. 37,468
RONALD YIN,	Reg. No. 27,607
BARRY N. YOUNG	Reg. No. 27,744

21

GT\6252046.1
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I hereby authorize and request insertion of the application number of the Application when officially known.

Direct all telephone calls to:

LISA A. HAILE, PH.D.
Telephone: (858) 677-1456

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LISA A. HAILE, PH.D.
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San Diego, CA 92121

Max-Planck-Gesellschaft zur Forderung der Wissenshaften e.V.

By:	Christa Herzog
Name:	Christa Herzog
Title:	Head of Patent Department
Date:	Sept. 5. 2001

Residence: Migdal David 7/..., 71700 Modi'in, Israel ILX

Citizenship: Israeli

Post Office Address: (Same as above)

4-00

Full name of fourth inventor: Yael Stein-Bach

Inventor's signature: Bach Yael

Date: 16.10.01

Residence: Etzel 25/7, 93714 Jerusalem, Israel ILX

Citizenship: Israeli

Post Office Address: (Same as above)

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Arg Lys Pro Cys Asp Thr Met Lys Val Gly Gly Asn Leu Asp Ser Lys
            740                 745                 750

Gly Tyr Gly Val Ala Thr Pro Lys Gly Ser Ser Leu Arg Thr Pro Val
        755                 760                 765

Asn Leu Ala Val Leu Lys Leu Ser Glu Ala Gly Val Leu Asp Lys Leu
    770                 775                 780

Lys Asn Lys Trp Trp Tyr Asp Lys Gly Glu Cys Gly Pro Lys Asp Ser
785                 790                 795                     800

Gly Ser Lys Asp Lys Thr Ser Ala Leu Ser Leu Ser Asn Val Ala Gly
                805                 810                 815

Val Phe Tyr Ile Leu Val Gly Gly Leu Gly Leu Ala Met Leu Val Ala
            820                 825                 830

Leu Ile Glu Phe Cys Tyr Lys Ser Arg Ala Glu Ala Lys Arg Met Lys
        835                 840                 845

Leu Thr Phe Ser Glu Ala Ile Arg Asn Lys Ala Arg Leu Ser Ile Thr
    850                 855                 860

Gly Ser Val Gly Glu Asn Gly Arg Val Leu Thr Pro Asp Cys Pro Lys
865                 870                 875                     880
```

```
Ala Val His Thr Gly Thr Ala Ile Arg Gln Ser Ser Gly Leu Ala Val
                885                 890                 895

Ile Ala Ser Asp Leu Pro
            900
```

<210> 5
<211> 1043
<212> PRT
<213> Homo sapiens

<400> 5

```
Met Gln His Ile Phe Ala Phe Phe Cys Thr Gly Phe Leu Gly Ala Val
  1               5                  10                  15

Val Gly Ala Asn Phe Pro Asn Asn Ile Gln Ile Gly Gly Leu Phe Pro
             20                  25                  30

Asn Gln Gln Ser Gln Glu His Ala Ala Phe Arg Phe Ala Leu Ser Gln
         35                  40                  45

Leu Thr Glu Pro Pro Lys Leu Leu Pro Gln Ile Asp Ile Val Asn Ile
     50                  55                  60

Ser Asp Thr Phe Glu Met Thr Tyr Arg Phe Cys Ser Gln Phe Ser Lys
 65                  70                  75                  80

Gly Val Tyr Ala Ile Phe Gly Phe Tyr Glu Arg Arg Thr Val Asn Met
                 85                  90                  95

Leu Thr Ser Phe Cys Gly Ala Leu His Val Cys Phe Ile Thr Pro Ser
            100                 105                 110

Phe Pro Val Asp Thr Ser Asn Gln Phe Val Leu Gln Leu Arg Pro Glu
        115                 120                 125

Leu Gln Asp Ala Leu Ile Ser Ile Ile Asp His Tyr Lys Trp Gln Lys
    130                 135                 140

Phe Val Tyr Ile Tyr Asp Ala Asp Arg Gly Leu Ser Val Leu Gln Lys
145                 150                 155                 160

Val Leu Asp Thr Ala Ala Glu Lys Asn Trp Gln Val Thr Ala Val Asn
                165                 170                 175

Ile Leu Thr Thr Thr Glu Glu Gly Tyr Arg Met Leu Phe Gln Asp Leu
            180                 185                 190

Glu Lys Lys Lys Glu Arg Leu Val Val Val Asp Cys Glu Ser Glu Arg
        195                 200                 205

Leu Asn Ala Ile Leu Gly Gln Ile Ile Lys Leu Glu Lys Asn Gly Ile
    210                 215                 220

Gly Tyr His Tyr Ile Leu Ala Asn Leu Gly Phe Met Asp Ile Asp Leu
225                 230                 235                 240
```

Asn Lys Phe Lys Glu Ser Gly Ala Asn Val Thr Gly Phe Gln Leu Val
245 250 255

Asn Tyr Thr Asp Thr Ile Pro Ala Lys Ile Met Gln Gln Trp Lys Asn
260 265 270

Ser Asp Ala Arg Asp His Thr Arg Val Asp Trp Lys Arg Pro Lys Tyr
275 280 285

Thr Ser Ala Leu Thr Tyr Asp Gly Val Lys Val Met Ala Glu Ala Phe
290 295 300

Gln Ser Leu Arg Arg Gln Arg Ile Asp Ile Ser Arg Arg Gly Asn Ala
305 310 315 320

Gly Asp Cys Leu Ala Asn Pro Ala Val Pro Trp Gly Gln Gly Ile Asp
325 330 335

Ile Gln Arg Ala Leu Gln Gln Val Arg Phe Glu Gly Leu Thr Gly Asn
340 345 350

Val Gln Phe Asn Glu Lys Gly Arg Arg Thr Asn Tyr Thr Leu His Val
355 360 365

Ile Glu Met Lys His Asp Gly Ile Arg Lys Ile Gly Tyr Trp Asn Glu
370 375 380

Asp Asp Lys Phe Val Pro Ala Ala Thr Asp Ala Gln Ala Gly Gly Asp
385 390 395 400

Asn Ser Ser Val Gln Asn Arg Thr Tyr Ile Val Thr Thr Ile Leu Glu
405 410 415

Asp Pro Tyr Val Met Leu Lys Lys Asn Ala Asn Gln Phe Glu Gly Asn
420 425 430

Asp Arg Tyr Glu Gly Tyr Cys Val Glu Leu Ala Ala Glu Ile Ala Lys
435 440 445

His Val Gly Tyr Ser Tyr Arg Leu Glu Ile Val Ser Asp Gly Lys Tyr
450 455 460

Gly Ala Arg Asp Pro Asp Thr Lys Ala Trp Asn Gly Met Val Gly Glu
465 470 475 480

Leu Val Tyr Gly Arg Ala Asp Val Ala Val Ala Pro Leu Thr Ile Thr
485 490 495

Leu Val Arg Glu Glu Val Ile Asp Phe Ser Lys Pro Phe Met Ser Leu
500 505 510

Gly Ile Ser Ile Met Ile Lys Lys Pro Gln Lys Ser Lys Pro Gly Val
515 520 525

Phe Ser Phe Leu Asp Pro Leu Ala Tyr Glu Ile Trp Met Cys Ile Val
530 535 540

Phe Ala Tyr Ile Gly Val Ser Val Val Leu Phe Leu Val Ser Arg Phe
545 550 555 560

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Ser Pro Tyr Glu Trp His Ser Glu Glu Phe Glu Glu Gly Arg Asp Gln
                565                 570                 575

Thr Thr Ser Asp Gln Ser Asn Glu Phe Gly Ile Phe Asn Ser Leu Trp
            580                 585                 590

Phe Ser Leu Gly Ala Phe Met Gln Gln Gly Cys Asp Ile Ser Pro Arg
        595                 600                 605

Ser Leu Ser Gly Arg Ile Val Gly Gly Val Trp Trp Phe Phe Thr Leu
    610                 615                 620

Ile Ile Ile Ser Ser Tyr Thr Ala Asn Leu Ala Ala Phe Leu Thr Val
625                 630                 635                 640

Glu Arg Met Val Ser Pro Ile Glu Ser Ala Glu Asp Leu Ala Asn Glu
                645                 650                 655

Thr Glu Ile Ala Tyr Gly Thr Leu Glu Ala Gly Ser Thr Lys Glu Phe
            660                 665                 670

Phe Arg Arg Ser Lys Ile Ala Val Phe Glu Lys Met Trp Thr Tyr Met
        675                 680                 685

Lys Ser Ala Glu Pro Ser Val Phe Val Arg Thr Thr Glu Glu Gly Met
    690                 695                 700

Ile Arg Val Arg Lys Ser Lys Gly Lys Tyr Ala Tyr Leu Leu Glu Ser
705                 710                 715                 720

Thr Met Asn Glu Tyr Ile Glu Gln Arg Lys Pro Cys Asp Thr Met Lys
                725                 730                 735

Val Gly Gly Asn Leu Asp Ser Lys Gly Tyr Gly Ile Ala Thr Pro Lys
            740                 745                 750

Gly Ser Ala Leu Arg Gly Pro Val Asn Leu Ala Val Leu Lys Leu Ser
        755                 760                 765

Glu Gln Gly Val Leu Asp Lys Leu Lys Ser Lys Trp Trp Tyr Asp Lys
    770                 775                 780

Gly Glu Cys Gly Ser Lys Asp Ser Gly Ser Lys Asp Lys Thr Ser Ala
785                 790                 795                 800

Leu Ser Leu Ser Asn Val Ala Gly Val Phe Tyr Ile Leu Ile Gly Gly
                805                 810                 815

Leu Gly Leu Ala Met Leu Val Ala Leu Ile Glu Phe Cys Tyr Lys Ser
            820                 825                 830

Arg Ser Glu Ser Lys Arg Met Lys Gly Phe Cys Leu Ile Pro Gln Gln
        835                 840                 845

Ser Ile Asn Glu Ala Ile Arg Thr Ser Thr Leu Pro Arg Asn Ser Gly
    850                 855                 860

Ala Gly Ala Ser Ser Gly Gly Ser Gly Glu Asn Gly Arg Val Val Ser
865                 870                 875                 880
```

His Asp Phe Pro Lys Ser Met Gln Ser Ile Pro Cys Met Ser His Ser
885 890 895

Ser Gly Met Pro Leu Gly Ala Thr Gly Leu Leu Glu Gln Met Glu Thr
900 905 910

Pro Trp Gly Ala Gly Ser Gly Ser Pro Ala Pro Ser Gln Thr Leu Gln
915 920 925

Cys Gln Lys Gln Gln Gln Asn Arg Lys Arg Asn His His Gln Pro Leu
930 935 940

Arg Pro Gln Glu Gly Phe Asn Arg Phe Ser Arg Ile Glu Lys Pro Phe
945 950 955 960

Cys Cys Pro Phe Ser Phe Phe Asp Val Leu Ser Pro Phe Ser Val Cys
965 970 975

Val Arg Met Lys Lys His Cys Thr Ala Ile Arg Gly Glu Pro Cys Leu
980 985 990

Met Lys Pro Val Ser Leu Arg Val Glu Ser Leu Glu His Gly Asn Cys
995 1000 1005

Thr Val Leu Phe Phe Ser Cys Cys Val Leu Val Cys Ala Ile Phe Phe
1010 1015 1020

Leu Thr Asn Ile His Gly Leu Gln Val Leu Leu Gly Pro Phe Leu Leu
1025 1030 1035 1040

Leu Glu Phe

<210> 6
<211> 883
<212> PRT
<213> Homo sapiens

<400> 6
Met Gln Lys Ile Met His Val Ser Val Leu Leu Ser Pro Val Leu Trp
1 5 10 15

Gly Leu Ile Phe Gly Val Ser Ser Asn Ser Ile Gln Ile Gly Gly Leu
20 25 30

Phe Pro Arg Gly Ala Asp Gln Glu Tyr Ser Ala Phe Arg Val Gly Met
35 40 45

Val Gln Phe Ser Thr Ser Glu Phe Arg Leu Thr Pro His Ile Asp Asn
50 55 60

Leu Glu Val Ala Asn Ser Phe Ala Val Thr Asn Ala Phe Cys Ser Gln
65 70 75 80

Phe Ser Arg Gly Val Tyr Ala Ile Phe Gly Phe Tyr Asp Lys Lys Ser
85 90 95

Val Asn Thr Ile Thr Ser Phe Cys Gly Thr Leu His Val Ser Phe Ile

100 105 110

Thr Pro Ser Phe Pro Thr Asp Gly Thr His Pro Phe Val Ile Gln Met
115 120 125

Arg Pro Asp Leu Lys Gly Ala Leu Leu Ser Leu Ile Glu Tyr Tyr Gln
130 135 140

Trp Asp Lys Phe Ala Tyr Leu Tyr Asp Ser Asp Arg Gly Leu Ser Thr
145 150 155 160

Leu Gln Ala Val Leu Asp Ser Ala Ala Glu Lys Lys Trp Gln Val Thr
165 170 175

Ala Ile Asn Val Gly Asn Ile Asn Asn Asp Lys Lys Asp Glu Met Tyr
180 185 190

Arg Ser Leu Phe Gln Asp Leu Glu Leu Lys Lys Glu Arg Arg Val Ile
195 200 205

Leu Asp Cys Glu Arg Asp Lys Val Asn Asp Ile Val Asp Gln Val Ile
210 215 220

Thr Ile Gly Lys His Val Lys Gly Tyr His Tyr Ile Ile Ala Asn Leu
225 230 235 240

Gly Phe Thr Asp Gly Asp Leu Leu Lys Ile Gln Phe Gly Gly Ala Asn
245 250 255

Val Ser Gly Phe Gln Ile Val Asp Tyr Asp Asp Ser Leu Val Ser Lys
260 265 270

Phe Ile Glu Arg Trp Ser Thr Leu Glu Glu Lys Glu Tyr Pro Gly Ala
275 280 285

His Thr Thr Thr Ile Lys Tyr Thr Ser Ala Leu Thr Tyr Asp Ala Val
290 295 300

Gln Val Met Thr Glu Ala Phe Arg Asn Leu Arg Lys Gln Arg Ile Glu
305 310 315 320

Ile Ser Arg Arg Gly Asn Ala Gly Asp Cys Leu Ala Asn Pro Ala Val
325 330 335

Pro Trp Gly Gln Gly Val Glu Ile Glu Arg Ala Leu Lys Gln Val Gln
340 345 350

Val Glu Gly Leu Ser Gly Asn Ile Lys Phe Asp Gln Asn Gly Lys Arg
355 360 365

Ile Asn Tyr Thr Ile Asn Ile Met Glu Leu Lys Thr Asn Gly Pro Arg
370 375 380

Lys Ile Gly Tyr Trp Ser Glu Val Asp Lys Met Val Val Thr Leu Thr
385 390 395 400

Glu Leu Pro Ser Gly Asn Asp Thr Ser Gly Leu Glu Asn Lys Thr Val
405 410 415

Val Val Thr Thr Ile Leu Glu Ser Pro Tyr Val Met Met Lys Lys Asn

420 425 430

His Glu Met Leu Glu Gly Asn Glu Arg Tyr Glu Gly Tyr Cys Val Asp
435 440 445

Leu Ala Ala Glu Ile Ala Lys His Cys Gly Phe Lys Tyr Lys Leu Thr
450 455 460

Ile Val Gly Asp Gly Lys Tyr Gly Ala Arg Asp Ala Asp Thr Lys Ile
465 470 475 480

Trp Asn Gly Met Val Gly Glu Leu Val Tyr Gly Lys Ala Asp Ile Ala
485 490 495

Ile Ala Pro Leu Thr Ile Thr Leu Val Arg Glu Glu Val Ile Asp Phe
500 505 510

Ser Lys Pro Phe Met Ser Leu Gly Ile Ser Ile Met Ile Lys Lys Pro
515 520 525

Gln Lys Ser Lys Pro Gly Val Phe Ser Phe Leu Asp Pro Leu Ala Tyr
530 535 540

Glu Ile Trp Met Cys Ile Val Phe Ala Tyr Ile Gly Val Ser Val Val
545 550 555 560

Leu Phe Leu Val Ser Arg Phe Ser Pro Tyr Glu Trp His Thr Glu Glu
565 570 575

Phe Glu Asp Gly Arg Glu Thr Gln Ser Ser Glu Ser Thr Asn Glu Phe
580 585 590

Gly Ile Phe Asn Ser Leu Trp Phe Ser Leu Gly Ala Phe Met Arg Gln
595 600 605

Gly Cys Asp Ile Ser Pro Arg Ser Leu Ser Gly Arg Ile Val Gly Gly
610 615 620

Val Trp Trp Phe Phe Thr Leu Ile Ile Ile Ser Ser Tyr Thr Ala Asn
625 630 635 640

Leu Ala Ala Phe Leu Thr Val Glu Arg Met Val Ser Pro Ile Glu Ser
645 650 655

Ala Glu Asp Leu Ser Lys Gln Thr Glu Ile Ala Tyr Gly Thr Leu Asp
660 665 670

Ser Gly Ser Thr Lys Glu Phe Phe Arg Arg Ser Lys Ile Ala Val Phe
675 680 685

Asp Lys Met Trp Thr Tyr Met Arg Ser Ala Glu Pro Ser Val Phe Val
690 695 700

Arg Thr Thr Ala Glu Gly Val Ala Arg Val Arg Lys Ser Lys Gly Lys
705 710 715 720

Tyr Ala Tyr Leu Leu Glu Ser Thr Met Asn Glu Tyr Ile Glu Gln Arg
725 730 735

Lys Pro Cys Asp Thr Met Lys Val Gly Gly Asn Leu Asp Ser Lys Gly

740 745 750

Tyr Gly Ile Ala Thr Pro Lys Gly Ser Ser Leu Arg Asn Ala Val Asn
755 760 765

Leu Ala Val Leu Lys Leu Asn Glu Gln Gly Leu Leu Asp Lys Leu Lys
770 775 780

Asn Lys Trp Trp Tyr Asp Lys Gly Glu Cys Gly Ser Gly Gly Gly Asp
785 790 795 800

Ser Lys Glu Lys Thr Ser Ala Leu Ser Leu Ser Asn Val Ala Gly Val
805 810 815

Phe Tyr Ile Leu Val Gly Gly Leu Gly Leu Ala Met Leu Val Ala Leu
820 825 830

Ile Glu Phe Cys Tyr Lys Ser Arg Ala Glu Ala Lys Arg Met Lys Val
835 840 845

Ala Lys Asn Ala Gln Asn Ile Asn Pro Ser Ser Ser Gln Asn Ser Gln
850 855 860

Asn Phe Ala Thr Tyr Lys Glu Gly Tyr Asn Val Tyr Gly Ile Glu Ser
865 870 875 880

Val Lys Ile

<210> 7
<211> 894
<212> PRT
<213> Homo sapiens

<400> 7
Met Ala Arg Gln Lys Lys Met Gly Gln Ser Val Leu Arg Ala Val Phe
1 5 10 15

Phe Leu Val Leu Gly Leu Leu Gly His Ser His Gly Gly Phe Pro Asn
20 25 30

Thr Ile Ser Ile Gly Gly Leu Phe Met Arg Asn Thr Val Gln Glu His
35 40 45

Ser Ala Phe Arg Phe Ala Val Gln Leu Tyr Asn Thr Asn Gln Asn Thr
50 55 60

Thr Glu Lys Pro Phe His Leu Asn Tyr His Val Asp His Leu Asp Ser
65 70 75 80

Ser Asn Ser Phe Ser Val Thr Asn Ala Phe Cys Ser Gln Phe Ser Arg
85 90 95

Gly Val Tyr Ala Ile Phe Gly Phe Tyr Asp Gln Met Ser Met Asn Thr
100 105 110

Leu Thr Ser Phe Cys Gly Ala Leu His Thr Ser Phe Val Thr Pro Ser
115 120 125

```
Phe Pro Thr Asp Ala Asp Val Gln Phe Val Ile Gln Met Arg Pro Ala
    130                 135                 140

Leu Lys Gly Ala Ile Leu Ser Leu Leu Gly His Tyr Lys Trp Glu Lys
145                 150                 155                 160

Phe Val Tyr Leu Tyr Asp Thr Glu Arg Gly Phe Ser Ile Leu Gln Ala
                165                 170                 175

Ile Met Glu Ala Ala Val Gln Asn Asn Trp Gln Val Thr Ala Arg Ser
            180                 185                 190

Val Gly Asn Ile Lys Asp Val Gln Glu Phe Arg Arg Ile Ile Glu Glu
        195                 200                 205

Met Asp Arg Arg Gln Glu Lys Arg Tyr Leu Ile Asp Cys Glu Val Glu
    210                 215                 220

Arg Ile Asn Thr Ile Leu Glu Gln Val Val Ile Leu Gly Lys His Ser
225                 230                 235                 240

Arg Gly Tyr His Tyr Met Leu Ala Asn Leu Gly Phe Thr Asp Ile Leu
                245                 250                 255

Leu Glu Arg Val Met His Gly Gly Ala Asn Ile Thr Gly Phe Gln Ile
            260                 265                 270

Val Asn Asn Glu Asn Pro Met Val Gln Gln Phe Ile Gln Arg Trp Val
        275                 280                 285

Arg Leu Asp Glu Arg Glu Phe Pro Glu Ala Lys Asn Ala Pro Leu Lys
    290                 295                 300

Tyr Thr Ser Ala Leu Thr His Asp Ala Ile Leu Val Ile Ala Glu Ala
305                 310                 315                 320

Phe Arg Tyr Leu Arg Arg Gln Arg Val Asp Val Ser Arg Arg Gly Ser
                325                 330                 335

Ala Gly Asp Cys Leu Ala Asn Pro Ala Val Pro Trp Ser Gln Gly Ile
            340                 345                 350

Asp Ile Glu Arg Ala Leu Lys Met Val Gln Val Gln Gly Met Thr Gly
        355                 360                 365

Asn Ile Gln Phe Asp Thr Tyr Gly Arg Arg Thr Asn Tyr Thr Ile Asp
    370                 375                 380

Val Tyr Glu Met Lys Val Ser Gly Ser Arg Lys Ala Gly Tyr Trp Asn
385                 390                 395                 400

Glu Tyr Glu Arg Phe Val Pro Phe Ser Asp Gln Gln Ile Ser Asn Asp
                405                 410                 415

Ser Ala Ser Ser Glu Asn Arg Thr Ile Val Val Thr Thr Ile Leu Glu
            420                 425                 430

Ser Pro Tyr Val Met Tyr Lys Lys Asn His Glu Gln Leu Glu Gly Asn
        435                 440                 445
```

Glu Arg Tyr Glu Gly Tyr Cys Val Asp Leu Ala Tyr Glu Ile Ala Lys
450 455 460

His Val Arg Ile Lys Tyr Lys Leu Ser Ile Val Gly Asp Gly Lys Tyr
465 470 475 480

Gly Ala Arg Asp Pro Glu Thr Lys Ile Trp Asn Gly Met Val Gly Glu
485 490 495

Leu Val Tyr Gly Arg Ala Asp Ile Ala Val Ala Pro Leu Thr Ile Thr
500 505 510

Leu Val Arg Glu Glu Val Ile Asp Phe Ser Lys Pro Phe Met Ser Leu
515 520 525

Gly Ile Ser Ile Met Ile Lys Lys Pro Gln Lys Ser Lys Pro Gly Val
530 535 540

Phe Ser Phe Leu Asp Pro Leu Ala Tyr Glu Ile Trp Met Cys Ile Val
545 550 555 560

Phe Ala Tyr Ile Gly Val Ser Val Val Leu Phe Leu Val Ser Arg Phe
565 570 575

Ser Pro Tyr Glu Trp His Leu Glu Asp Asn Asn Glu Glu Pro Arg Asp
580 585 590

Pro Gln Ser Pro Pro Asp Pro Pro Asn Glu Phe Gly Ile Phe Asn Ser
595 600 605

Leu Trp Phe Ser Leu Gly Ala Phe Met Gln Gln Gly Cys Asp Ile Ser
610 615 620

Pro Arg Ser Leu Ser Gly Arg Ile Val Gly Gly Val Trp Trp Phe Phe
625 630 635 640

Thr Leu Ile Ile Ile Ser Ser Tyr Thr Ala Asn Leu Ala Ala Phe Leu
645 650 655

Thr Val Glu Arg Met Val Ser Pro Ile Glu Ser Ala Glu Asp Leu Ala
660 665 670

Lys Gln Thr Glu Ile Ala Tyr Gly Thr Leu Asp Ser Gly Ser Thr Lys
675 680 685

Glu Phe Phe Arg Arg Ser Lys Ile Ala Val Tyr Glu Lys Met Trp Ser
690 695 700

Tyr Met Lys Ser Ala Glu Pro Ser Val Phe Thr Lys Thr Thr Ala Asp
705 710 715 720

Gly Val Ala Arg Val Arg Lys Ser Lys Gly Lys Phe Ala Phe Leu Leu
725 730 735

Glu Ser Thr Met Asn Glu Tyr Ile Glu Gln Arg Lys Pro Cys Asp Thr
740 745 750

Met Lys Val Gly Gly Asn Leu Asp Ser Lys Gly Tyr Gly Val Ala Thr
755 760 765

```
Pro Lys Gly Ser Ala Leu Gly Asn Ala Val Asn Leu Ala Val Leu Lys
    770                 775                 780

Leu Asn Glu Gln Gly Leu Leu Asp Lys Leu Lys Asn Lys Trp Trp Tyr
785                 790                 795                 800

Asp Lys Gly Glu Cys Gly Ser Gly Gly Gly Asp Ser Lys Asp Lys Thr
                805                 810                 815

Ser Ala Leu Ser Leu Ser Asn Val Ala Gly Val Phe Tyr Ile Leu Val
            820                 825                 830

Gly Gly Leu Gly Leu Ala Met Met Val Ala Leu Ile Glu Phe Cys Tyr
        835                 840                 845

Lys Ser Arg Ala Glu Ser Lys Arg Met Lys Leu Thr Lys Asn Thr Gln
    850                 855                 860

Asn Phe Lys Pro Ala Pro Ala Thr Asn Thr Gln Asn Tyr Ala Thr Tyr
865                 870                 875                 880

Arg Glu Gly Tyr Asn Val Tyr Gly Thr Glu Ser Val Lys Ile
                885                 890


<210> 8
<211> 902
<212> PRT
<213> Homo sapiens

<400> 8
Met Arg Ile Ile Ser Arg Gln Ile Val Leu Leu Phe Ser Gly Phe Trp
  1               5                  10                  15

Gly Leu Ala Met Gly Ala Phe Pro Ser Ser Val Gln Ile Gly Gly Leu
             20                  25                  30

Phe Ile Arg Asn Thr Asp Gln Glu Tyr Thr Ala Phe Arg Leu Ala Ile
         35                  40                  45

Phe Leu His Asn Thr Ala Pro Asn Ala Ser Glu Ala Pro Phe Asn Leu
     50                  55                  60

Val Pro His Val Asp Asn Ile Glu Thr Ala Asn Ser Phe Ala Val Thr
 65                  70                  75                  80

Asn Ala Phe Cys Ser Gln Tyr Ser Arg Gly Val Phe Ala Ile Phe Gly
                 85                  90                  95

Leu Tyr Asp Lys Arg Ser Val His Thr Leu Thr Ser Phe Cys Ser Ala
            100                 105                 110

Leu His Ile Ser Leu Ile Thr Pro Ser Phe Pro Thr Glu Gly Glu Ser
        115                 120                 125

Gln Phe Val Leu Gln Leu Arg Pro Ser Leu Arg Gly Ala Leu Leu Ser
    130                 135                 140
```

Leu Leu Asp His Tyr Glu Trp Asn Cys Phe Val Phe Leu Tyr Asp Thr
145 150 155 160

Asp Arg Gly Tyr Ser Ile Leu Gln Ala Ile Met Glu Lys Ala Gly Gln
165 170 175

Asn Gly Trp His Val Ser Ala Ile Cys Val Glu Asn Phe Asn Asp Val
180 185 190

Ser Tyr Arg Gln Leu Leu Glu Glu Leu Asp Arg Arg Gln Glu Lys Lys
195 200 205

Phe Val Ile Asp Cys Glu Ile Glu Arg Leu Gln Asn Ile Leu Glu Gln
210 215 220

Ile Val Ser Val Gly Lys His Val Lys Gly Tyr His Tyr Ile Ile Ala
225 230 235 240

Asn Leu Gly Phe Lys Asp Ile Ser Leu Glu Arg Phe Ile His Gly Gly
245 250 255

Ala Asn Val Thr Gly Phe Gln Leu Val Asp Phe Asn Thr Pro Met Val
260 265 270

Thr Lys Leu Met Asp Arg Trp Lys Lys Leu Asp Gln Arg Glu Tyr Pro
275 280 285

Gly Ser Glu Thr Pro Pro Lys Tyr Thr Ser Ala Leu Thr Tyr Asp Gly
290 295 300

Val Leu Val Met Ala Glu Thr Phe Arg Ser Leu Arg Arg Gln Lys Ile
305 310 315 320

Asp Ile Ser Arg Arg Gly Lys Ser Gly Asp Cys Leu Ala Asn Pro Ala
325 330 335

Ala Pro Trp Gly Gln Gly Ile Asp Met Glu Arg Thr Leu Lys Gln Val
340 345 350

Arg Ile Gln Gly Leu Thr Gly Asn Val Gln Phe Asp His Tyr Gly Arg
355 360 365

Arg Val Asn Tyr Thr Met Asp Val Phe Glu Leu Lys Ser Thr Gly Pro
370 375 380

Arg Lys Val Gly Tyr Trp Asn Asp Met Asp Lys Leu Val Leu Ile Gln
385 390 395 400

Asp Val Pro Thr Leu Gly Asn Asp Thr Ala Ala Ile Glu Asn Arg Thr
405 410 415

Val Val Val Thr Thr Ile Met Glu Ser Pro Tyr Val Met Tyr Lys Lys
420 425 430

Asn His Glu Met Phe Glu Gly Asn Asp Lys Tyr Glu Gly Tyr Cys Val
435 440 445

Asp Leu Ala Ser Glu Ile Ala Lys His Ile Gly Ile Lys Tyr Lys Ile
450 455 460

```
Ala Ile Val Pro Asp Gly Lys Tyr Gly Ala Arg Asp Ala Asp Thr Lys
465                 470                 475                 480

Ile Trp Asn Gly Met Val Gly Glu Leu Val Tyr Gly Lys Ala Glu Ile
                485                 490                 495

Ala Ile Ala Pro Leu Thr Ile Thr Leu Val Arg Glu Glu Val Ile Asp
            500                 505                 510

Phe Ser Lys Pro Phe Met Ser Leu Gly Ile Ser Ile Met Ile Lys Lys
        515                 520                 525

Pro Gln Lys Ser Lys Pro Gly Val Phe Ser Phe Leu Asp Pro Leu Ala
    530                 535                 540

Tyr Glu Ile Trp Met Cys Ile Val Phe Ala Tyr Ile Gly Val Ser Val
545                 550                 555                 560

Val Leu Phe Leu Val Ser Arg Phe Ser Pro Tyr Glu Trp His Thr Glu
                565                 570                 575

Glu Pro Glu Asp Gly Lys Glu Gly Pro Ser Asp Gln Pro Pro Asn Glu
            580                 585                 590

Phe Gly Ile Phe Asn Ser Leu Trp Phe Ser Leu Gly Ala Phe Met Gln
        595                 600                 605

Gln Gly Cys Asp Ile Ser Pro Arg Ser Leu Ser Gly Arg Ile Val Gly
    610                 615                 620

Gly Val Trp Trp Phe Phe Thr Leu Ile Ile Ile Ser Ser Tyr Thr Ala
625                 630                 635                 640

Asn Leu Ala Ala Phe Leu Thr Val Glu Arg Met Val Ser Pro Ile Glu
                645                 650                 655

Ser Ala Glu Asp Leu Ala Lys Gln Thr Glu Ile Ala Tyr Gly Thr Leu
            660                 665                 670

Asp Ser Gly Ser Thr Lys Glu Phe Phe Arg Arg Ser Lys Ile Ala Val
        675                 680                 685

Tyr Glu Lys Met Trp Thr Tyr Met Arg Ser Ala Glu Pro Ser Val Phe
    690                 695                 700

Thr Arg Thr Thr Ala Glu Gly Val Ala Arg Val Arg Lys Ser Lys Gly
705                 710                 715                 720

Lys Phe Ala Phe Leu Leu Glu Ser Thr Met Asn Asp Asn Ile Glu Gln
                725                 730                 735

Arg Lys Pro Cys Asp Thr Met Lys Val Gly Gly Asn Leu Asp Ser Lys
            740                 745                 750

Gly Tyr Gly Val Ala Thr Pro Lys Gly Ser Ser Leu Arg Thr Pro Val
        755                 760                 765

Asn Leu Ala Val Leu Lys Leu Ser Glu Ala Gly Val Leu Asp Lys Leu
    770                 775                 780
```

```
Lys Asn Lys Trp Trp Tyr Asp Lys Gly Glu Cys Gly Pro Lys Asp Ser
785                 790                 795                 800

Gly Ser Lys Asp Lys Thr Ser Ala Leu Ser Leu Ser Asn Val Ala Gly
                805                 810                 815

Val Phe Tyr Ile Leu Val Gly Gly Leu Gly Leu Ala Met Leu Val Ala
            820                 825                 830

Leu Ile Glu Phe Cys Tyr Lys Ser Arg Ala Glu Ala Lys Arg Met Lys
        835                 840                 845

Leu Thr Phe Ser Glu Ala Ile Arg Asn Lys Ala Arg Leu Ser Ile Thr
    850                 855                 860

Gly Ser Val Gly Glu Asn Gly Arg Val Leu Thr Pro Asp Cys Pro Lys
865                 870                 875                 880

Ala Val His Thr Gly Thr Ala Ile Arg Gln Ser Ser Gly Leu Ala Val
                885                 890                 895

Ile Ala Ser Asp Leu Pro
            900
```

```
<210> 9
<211> 907
<212> PRT
<213> Mus musculus

<400> 9
Met Pro Tyr Ile Phe Ala Phe Phe Cys Thr Gly Phe Leu Gly Ala Val
  1               5                  10                  15

Val Gly Ala Asn Phe Pro Asn Asn Ile Gln Ile Gly Gly Leu Phe Pro
            20                  25                  30

Asn Gln Gln Ser Gln Glu His Ala Ala Phe Arg Phe Ala Leu Ser Gln
        35                  40                  45

Leu Thr Glu Pro Pro Lys Leu Leu Pro Gln Ile Asp Ile Val Asn Ile
    50                  55                  60

Ser Asp Ser Phe Glu Met Thr Tyr Arg Phe Cys Ser Gln Phe Ser Lys
 65                  70                  75                  80

Gly Val Tyr Ala Ile Phe Gly Phe Tyr Glu Arg Arg Thr Val Asn Met
                85                  90                  95

Leu Thr Ser Phe Cys Gly Ala Leu His Val Cys Phe Ile Thr Pro Ser
            100                 105                 110

Phe Pro Val Asp Thr Ser Asn Gln Phe Val Leu Gln Leu Arg Pro Glu
        115                 120                 125

Leu Gln Glu Ala Leu Ile Ser Ile Ile Asp His Tyr Lys Trp Gln Thr
    130                 135                 140

Phe Val Tyr Ile Tyr Asp Ala Asp Arg Gly Leu Ser Val Leu Gln Arg
```

```
145                 150                 155                 160

Val Leu Asp Thr Ala Ala Glu Lys Asn Trp Gln Val Thr Ala Val Asn
                165                 170                 175

Ile Leu Thr Thr Thr Glu Glu Gly Tyr Arg Met Leu Phe Gln Asp Leu
            180                 185                 190

Glu Lys Lys Lys Glu Arg Leu Val Val Val Asp Cys Glu Ser Glu Arg
        195                 200                 205

Leu Asn Ala Ile Leu Gly Gln Ile Val Lys Leu Glu Lys Asn Gly Ile
    210                 215                 220

Gly Tyr His Tyr Ile Leu Ala Asn Leu Gly Phe Met Asp Ile Asp Leu
225                 230                 235                 240

Asn Lys Phe Lys Glu Ser Gly Ala Asn Val Thr Gly Phe Gln Leu Val
                245                 250                 255

Asn Tyr Thr Asp Thr Ile Pro Ala Arg Ile Met Gln Gln Trp Arg Thr
            260                 265                 270

Ser Asp Ala Arg Asp His Thr Arg Val Asp Trp Lys Arg Pro Lys Tyr
        275                 280                 285

Thr Ser Ala Leu Thr Tyr Asp Gly Val Lys Val Met Ala Glu Ala Phe
    290                 295                 300

Gln Ser Leu Arg Arg Gln Arg Ile Asp Ile Ser Arg Arg Gly Asn Ala
305                 310                 315                 320

Gly Asp Cys Leu Ala Asn Pro Ala Val Pro Trp Gly Gln Gly Ile Asp
                325                 330                 335

Ile Gln Arg Ala Leu Gln Gln Val Arg Phe Glu Gly Leu Thr Gly Asn
            340                 345                 350

Val Gln Phe Asn Glu Lys Gly Arg Arg Thr Asn Tyr Thr Leu His Val
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Ile Glu Met Lys His Asp Gly Ile Arg Lys Ile Gly Tyr Trp Asn Glu
    370                 375                 380

Asp Asp Lys Phe Val Pro Ala Ala Thr Asp Ala Gln Ala Gly Gly Asp
385                 390                 395                 400

Asn Ser Ser Val Gln Asn Arg Thr Tyr Ile Val Thr Thr Ile Leu Glu
                405                 410                 415

Asp Pro Tyr Val Met Leu Lys Lys Asn Ala Asn Gln Phe Glu Gly Asn
            420                 425                 430

Asp Arg Tyr Glu Gly Tyr Cys Val Glu Leu Ala Ala Glu Ile Ala Lys
        435                 440                 445

His Val Gly Tyr Ser Tyr Arg Leu Glu Ile Val Ser Asp Gly Lys Tyr
    450                 455                 460

Gly Ala Arg Asp Pro Asp Thr Lys Ala Trp Asn Gly Met Val Gly Glu
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465 470 475 480

Leu Val Tyr Gly Arg Ala Asp Val Ala Val Ala Pro Leu Thr Ile Thr
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Leu Val Arg Glu Glu Val Ile Asp Phe Ser Lys Pro Phe Met Ser Leu
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Gly Ile Ser Ile Met Ile Lys Lys Pro Gln Lys Ser Lys Pro Gly Val
515 520 525

Phe Ser Phe Leu Asp Pro Leu Ala Tyr Glu Ile Trp Met Cys Ile Val
530 535 540

Phe Ala Tyr Ile Gly Val Ser Val Val Leu Phe Leu Val Ser Arg Phe
545 550 555 560

Ser Pro Tyr Glu Trp His Ser Glu Glu Phe Glu Glu Gly Arg Asp Gln
565 570 575

Thr Thr Ser Asp Gln Ser Asn Glu Phe Gly Ile Phe Asn Ser Leu Trp
580 585 590

Phe Ser Leu Gly Ala Phe Met Gln Gln Gly Cys Asp Ile Ser Pro Arg
595 600 605

Ser Leu Ser Gly Arg Ile Val Gly Gly Val Trp Trp Phe Phe Thr Leu
610 615 620

Ile Ile Ile Ser Ser Tyr Thr Ala Asn Leu Ala Ala Phe Leu Thr Val
625 630 635 640

Glu Arg Met Val Ser Pro Ile Glu Ser Ala Glu Asp Leu Ala Lys Gln
645 650 655

Thr Glu Ile Ala Tyr Gly Thr Leu Glu Ala Gly Ser Thr Lys Glu Phe
660 665 670

Phe Arg Arg Ser Lys Ile Ala Val Phe Glu Lys Met Trp Thr Tyr Met
675 680 685

Lys Ser Ala Glu Pro Ser Val Phe Val Arg Thr Thr Glu Glu Gly Met
690 695 700

Ile Arg Val Arg Lys Ser Lys Gly Lys Tyr Ala Tyr Leu Leu Glu Ser
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Thr Met Asn Glu Tyr Ile Glu Gln Arg Lys Pro Cys Asp Thr Met Lys
725 730 735

Val Gly Gly Asn Leu Asp Ser Lys Gly Tyr Gly Ile Ala Thr Pro Lys
740 745 750

Gly Ser Ala Leu Arg Gly Pro Val Asn Leu Ala Val Leu Lys Leu Ser
755 760 765

Glu Gln Gly Val Leu Asp Lys Leu Lys Ser Lys Trp Trp Tyr Asp Lys
770 775 780

Gly Glu Cys Gly Ser Lys Asp Ser Gly Ser Lys Asp Lys Thr Ser Ala

785 790 795 800

Leu Ser Leu Ser Asn Val Ala Gly Val Phe Tyr Ile Leu Ile Gly Gly
805 810 815

Leu Gly Leu Ala Met Leu Val Ala Leu Ile Glu Phe Cys Tyr Lys Ser
820 825 830

Arg Ser Glu Ser Lys Arg Met Lys Gly Phe Cys Leu Ile Pro Gln Gln
835 840 845

Ser Ile Asn Glu Ala Ile Arg Thr Ser Thr Leu Pro Arg Asn Ser Gly
850 855 860

Ala Gly Ala Ser Gly Gly Ser Gly Ser Gly Glu Asn Gly Arg Val Val
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Ser Ser Gly Met Pro Leu Gly Ala Thr Gly Leu
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<212> PRT
<213> Mus musculus

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Phe Pro Arg Gly Ala Asp Gln Glu Tyr Ser Ala Phe Arg Val Gly Met
35 40 45

Val Gln Phe Ser Thr Ser Glu Phe Arg Leu Thr Pro His Ile Asp Asn
50 55 60

Leu Glu Val Ala Asn Ser Phe Ala Val Thr Asn Ala Phe Cys Ser Gln
65 70 75 80

Phe Ser Arg Gly Val Tyr Ala Ile Phe Gly Phe Tyr Asp Lys Lys Ser
85 90 95

Val Asn Thr Ile Thr Ser Phe Cys Gly Thr Leu His Val Ser Phe Ile
100 105 110

Thr Pro Ser Phe Pro Thr Asp Gly Thr His Pro Phe Val Ile Gln Met
115 120 125

Arg Pro Asp Leu Lys Gly Ala Leu Leu Ser Leu Ile Glu Tyr Tyr Gln
130 135 140

Trp Asp Lys Phe Ala Tyr Leu Tyr Asp Ser Asp Arg Gly Leu Ser Thr
145 150 155 160

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Leu Gln Ala Val Leu Asp Ser Ala Ala Glu Lys Lys Trp Gln Val Thr
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Ala Ile Asn Val Gly Asn Ile Asn Asn Asp Lys Lys Asp Glu Thr Tyr
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Arg Ser Leu Phe Gln Asp Leu Glu Leu Lys Lys Glu Arg Arg Val Ile
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Leu Asp Cys Glu Arg Asp Lys Val Asn Asp Ile Val Asp Gln Val Ile
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Thr Ile Gly Lys His Val Lys Gly Tyr His Tyr Ile Ile Ala Asn Leu
225                 230                 235                 240

Gly Phe Thr Asp Gly Asp Leu Leu Lys Ile Gln Phe Gly Gly Ala Asn
                245                 250                 255

Val Ser Gly Phe Gln Ile Val Val Tyr Asp Asp Ser Leu Ala Ser Lys
            260                 265                 270

Phe Ile Glu Arg Trp Ser Thr Leu Glu Gly Lys Glu Tyr Pro Gly Ala
        275                 280                 285

His Thr Ala Thr Ile Lys Tyr Thr Ser Ala Leu Thr Tyr Asp Ala Val
    290                 295                 300

Gln Val Met Thr Glu Ala Phe Arg Asn Leu Arg Lys Gln Arg Ile Glu
305                 310                 315                 320

Ile Ser Arg Arg Gly Asn Ala Gly Asp Cys Leu Ala Asn Pro Ala Val
                325                 330                 335

Pro Trp Gly Gln Gly Val Glu Ile Glu Arg Ala Leu Lys Gln Val Gln
            340                 345                 350

Val Glu Gly Leu Ser Gly Asn Ile Lys Phe Asp Gln Asn Gly Lys Arg
        355                 360                 365

Ile Asn Tyr Thr Ile Asn Ile Met Glu Leu Lys Thr Asn Gly Pro Arg
    370                 375                 380

Lys Ile Gly Tyr Trp Ser Glu Val Asp Lys Met Val Val Thr Leu Thr
385                 390                 395                 400

Glu Leu Pro Ser Gly Asn Asp Thr Ser Gly Leu Glu Asn Lys Thr Val
                405                 410                 415

Val Val Thr Thr Ile Leu Glu Ser Pro Tyr Val Met Met Lys Lys Asn
            420                 425                 430

His Glu Met Leu Glu Gly Asn Glu Arg Tyr Glu Gly Tyr Cys Val Asp
        435                 440                 445

Leu Ala Ala Glu Ile Ala Lys His Cys Gly Phe Lys Tyr Lys Leu Thr
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Ile Val Gly Asp Gly Lys Tyr Gly Ala Arg Asp Ala Asp Thr Lys Ile
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Trp Asn Gly Met Val Gly Glu Leu Val Tyr Gly Lys Ala Asp Ile Ala
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Ile Ala Pro Leu Thr Ile Thr Leu Val Arg Glu Glu Val Ile Asp Phe
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Ser Lys Pro Phe Met Ser Leu Gly Ile Ser Ile Met Ile Lys Lys Pro
515 520 525

Gln Lys Ser Lys Pro Gly Val Phe Ser Phe Leu Asp Pro Leu Ala Tyr
530 535 540

Glu Ile Trp Met Cys Ile Val Phe Ala Tyr Ile Gly Val Ser Val Val
545 550 555 560

Leu Phe Leu Val Ser Arg Phe Ser Pro Tyr Glu Trp His Thr Glu Glu
565 570 575

Phe Glu Asp Gly Arg Glu Thr Gln Ser Ser Glu Ser Thr Asn Glu Phe
580 585 590

Gly Ile Phe Asn Ser Leu Trp Phe Ser Leu Gly Ala Phe Met Arg Gln
595 600 605

Gly Cys Asp Ile Ser Pro Arg Ser Leu Ser Gly Arg Ile Val Gly Gly
610 615 620

Val Trp Trp Phe Phe Thr Leu Ile Ile Ile Ser Ser Tyr Thr Ala Asn
625 630 635 640

Leu Ala Ala Phe Leu Thr Val Glu Arg Met Val Ser Pro Ile Glu Ser
645 650 655

Ala Glu Asp Leu Ser Lys Gln Thr Glu Ile Ala Tyr Gly Thr Leu Asp
660 665 670

Ser Gly Ser Thr Lys Glu Phe Phe Arg Arg Ser Lys Ile Ala Val Phe
675 680 685

Asp Lys Met Trp Thr Tyr Met Arg Ser Ala Glu Pro Ser Val Phe Val
690 695 700

Arg Thr Thr Ala Glu Gly Val Ala Arg Val Arg Lys Ser Lys Gly Lys
705 710 715 720

Tyr Ala Tyr Leu Leu Glu Ser Thr Met Asn Glu Tyr Ile Glu Gln Arg
725 730 735

Lys Pro Cys Asp Thr Met Lys Val Gly Gly Asn Leu Asp Ser Lys Gly
740 745 750

Tyr Gly Ile Ala Thr Pro Lys Gly Ser Ser Leu Gly Asn Ala Val Asn
755 760 765

Leu Ala Val Leu Lys Leu Asn Glu Gln Gly Leu Leu Asp Lys Leu Lys
770 775 780

Asn Lys Trp Trp Tyr Asp Lys Gly Glu Cys Gly Ser Gly Gly Gly Asp
785 790 795 800

Ser Lys Glu Lys Thr Ser Ala Leu Ser Leu Ser Asn Val Ala Gly Val
805 810 815

Phe Tyr Ile Leu Val Gly Gly Leu Gly Leu Ala Met Leu Val Ala Leu
820 825 830

Ile Glu Phe Cys Tyr Lys Ser Arg Ala Glu Ala Lys Arg Met Lys Val
835 840 845

Ala Lys Asn Ala Gln Asn Ile Asn Pro Ser Ser Ser Gln Asn Ser Gln
850 855 860

Asn Phe Ala Thr Tyr Lys Glu Gly Tyr Asn Val Tyr Gly Ile Glu Ser
865 870 875 880

Val Lys Ile

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<212> DNA
<213> Rattus norvegicus

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gcttttaggt ttgctttgtc acaactcacg gagcccccca agctgcttcc ccagatcgat 180
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wherein nnn codes for any aromatic amino acid

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&lt;211&gt; 2652
&lt;212&gt; DNA
&lt;213&gt; Rattus norvegicus

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wherein nnn codes for any aromatic amino acid

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<211> 2667
<212> DNA
<213> Rattus norvegicus

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aagcctgctc ctgccaccaa cactcagaat tacgctacat acagagaagg ctacaacgtg 2640
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wherein nnn codes for any aromatic amino acid

<210> 14
<211> 2709
<212> DNA
<213> Rattus norvegicus

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wherein nnn codes for any aromatic amino acid

<210> 15
<211> 2721
<212> DNA
<213> Homo sapiens

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wherein nnn codes for any aromatic amino acid

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<211> 2652
<212> DNA
<213> Homo sapiens

<400> 16
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wherein nnn codes for any aromatic amino acid

<210> 17
<211> 2685
<212> DNA
<213> Homo sapiens

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wherein nnn codes for any aromatic amino acid

<210> 18
<211> 2709
<212> DNA
<213> Homo sapiens

<400> 18
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wherein nnn codes for any aromatic amino acid

<210> 19
<211> 2724
<212> DNA
<213> Mus musculus

<400> 19

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wherein nnn codes for any aromatic amino acid

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<212> DNA
<213> Mus musculus

<400> 20

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wherein nnn codes for any aromatic amino acid

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<212> DNA
<213> Rattus norvegicus

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